The Neural Basis of the Episodic Retrieval of Emotional Memories

Adam Paul Richard Smith

2004

A thesis submitted to University College London for the degree of Doctor of Philosophy

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Abstract

There is considerable evidence that memory is enhanced for emotional events and items, reflecting the evolutionary importance of our ability to modify representations of the biological or social value of environmental elements, and react appropriately to them. Differences in the neural and cognitive processing of emotional and neutral memories have been the subject of much interest in neuroscientific research. Whilst many studies have focused on the role of emotion in modulating encoding and consolidation of memory, few have examined interactions between emotion and memory during retrieval. The aim of the work described in this thesis was to investigate neural activity associated with retrieval of emotional and neutral episodic memories using both event-related potentials and functional magnetic resonance imaging, such that activity could be determined with high temporal and spatial resolution. A series of experiments were carried out investigating retrieval activity associated with neutral items encoded in emotional or neutral contexts, thereby avoiding confounds associated with previous experiments directly comparing recognition of emotional and neutral stimuli. Firstly, the neural correlates of simple recognition of items from emotional and neutral contexts, where context was not task relevant, were characterised. Qualitatively dissociable patterns of activity were revealed during retrieval of emotional and neutral contexts, with emotion modulating both pre- and post-retrieval processing. Further experiments revealed distinct patterns of activity, most notably a lateralization of amygdala responses, differentiating successful from unsuccessful retrieval of emotional information. The importance of the relevance of emotional information to ongoing behaviour was also found to modulate patterns of retrieval activity. Finally, functional connectivity analyses revealed dynamic interactions between hippocampus, amygdala and medial orbitofrontal cortex underlying retrieval of emotional memories. These findings provide insights into the nature of the neural and cognitive processes supporting retrieval of emotional information, while using paradigms which avoid confounding mnemonic effects with online processing.

Acknowledgements

I am extremely grateful for the friendship, support and advice of all the members of the Institute of Cognitive Neuroscience, and the Functional Imaging Laboratory, particularly the members of the Cognitive Electrophysiology and Emotional Imaging groups with whom it has been a great pleasure to work. I am indebted to Mick and Ray for their willing and dedicated supervision, as well as their faith in letting me pursue my own course.

To my family, and all my friends, my heartfelt thanks.

Table of Contents

Foreword

And when thy slumbering conscience, fretting
By recollection's torturing flame,
Thou didst reveal the hideous setting
Of thy life's current ere I came:
When suddenly I saw thee sicken
And weeping, hide thine anguished face,
Revolted, Maddened, horror-stricken,
At memories of foul disgrace
(F. Dostoyevsky, Notes from the underground, 1864)

But last year's bitter loving must remain
Heaped on my heart, and my old thoughts abide.
There are a hundred places where I fear
To go, - so with his memory they brim.
And entering with relief some quiet place
Where never fell his boot or shone his face I say,
"There is no memory of him here!"
And so stand stricken, so remembering him.
(E.St.V. Millay, Time Does Not Bring Relief, 1939)

The power of past emotional events to pervade our consciousness and drive our thoughts and actions is underlined by many wonderful pieces of art and literature. The power of emotional symbolism in human culture reflects how fundamental to our viability is the ability to focus upon those aspects of the environment with greatest biological or social importance, and to react appropriately to them. Memory for past events of emotional significance lends flexibility to our affective reactions, allowing modifiable representations of value to be maintained and guiding our behaviour to maximise viability. The work presented in this thesis is a step towards delineating the neural mechanisms and cognitive processes subserving the retrieval of emotional

memories. The experiments described primarily address differences in the processes underlying retrieval of emotional and neutral events from episodic memory, although some of the effects observed may reflect modulation of implicit memory processes. One of the issues addressed whether the circuitry underlying retrieval of emotional and neutral memories differed when their retrieval was incidental to a memory task. Also investigated were differences between emotion effects on successfully and unsuccessfully recollected memories, and whether the nature of response requirements modified these effects. Finally, the issue of neural interactions and effective connectivity changes during retrieval of emotional memories was addressed.

This thesis is organised into three main sections. The first of these sections describes the theoretical background to the experiments described later. Firstly, there is an introduction to the cognitive neuroscience of memory, discussing the different types of memory processing, and how these can be tested experimentally. There follows a chapter describing our current understanding of interactions between the systems and processes underlying emotion and memory, and discussing the general approach taken to furthering our understanding of these issues in this thesis. Neural activity was measured using non-invasive functional imaging techniques, and the first part of chapter 3 sets out the principles of the techniques used, and highlights some considerations that must be made when using such techniques experimentally. The final part of the first section describes the general protocols adopted in the experiments described herein.

The second section of the thesis is concerned with experimental work. Chapters 4 and 5 describe neural activity associated with the incidental retrieval of emotional encoding contexts. Chapters 6 and 7 then examine activity under conditions where retrieval of emotional information is task-relevant, and compare the effects of emotion

when material is successfully recollected or not. Chapter 8 then attempts to probe interactions between neural structures supporting affective and mnemonic processing and determine how these change during emotion retrieval. Each chapter is preceded with an introduction relating specifically to the experimental question addressed, and ends with a discussion of the implications of the findings.

The final section of the thesis summarises the findings of the experimental work, and discusses the wider implications of the findings for our understanding of the mechanisms underlying retrieval of emotional episodic memories. This section also highlights outstanding issues and suggests some directions for future work.

Chapter 1 - Episodic Memory

Introduction

Memory, the modification of processing or behaviour as a result of past experience, is fundamental to the biological viability of almost all living organisms. Human memory has been extensively studied by researchers from a wide range of fields, and remains a highly dynamic area of research. In this chapter we will discuss some general concepts of memory, before focussing specifically on episodic memory, that is memory for specific personal events, and illuminating issues related to experimental design and the neuroanatomical substrates of episodic memory.

Multiple Memory Systems

The concept that memory may be fractionated into separate sub-systems, rather than being a unitary faculty, has been a key aspect of memory research over the last 50 years. The multiple component memory system hypothesis has a long history (Aristotle; James, 1890), but was first tied to neurophysiology by Hebb (1949) who proposed that short-term memory (STM) might be based upon ongoing electrical activity in the brain, whilst long-term memory (LTM) was dependent upon more permanent neurochemical changes. Evidence for such a distinction was found both in normal subjects, where prevention of rehearsal led to rapid forgetting of small amounts of presented materials (Brown, 1958; Peterson and Peterson, 1959), and in patients with brain damage. The most influential neuropsychological evidence for fractionation of memory came from patient H.M., a patient who developed severe

anterograde amnesia following bilateral resection of the medial temporal lobes (MTL) to treat intractable epilepsy (Scoville and Milner, 1957). Despite this severe memory impairment for events subsequent to the operation (and to some extent for events prior to it) there was relative sparing of other cognitive abilities, such as language, intellect and short-term memory (for review of similar cases see Scoville and Correl, 1973). In contrast, subsequent studies reported impaired STM with relative sparing of LTM in patients with lesions in the left parietal lobe (Shallice and Warrington, 1970; Butterworth et al, 1996; see Markowitsch et al, 1999 for review). Such a double-dissociation provides strong evidence for separable systems for STM and LTM, notwithstanding issues relating to the roles which particular brain regions serve in mnemonic processing. Further research provided evidence for further distinction within both STM (see Baddeley and Hitch, 1974) and LTM, on which we will focus here.

Much of the fractionation of LTM has derived from work with patients suffering from the 'classic' amnesic syndrome, which is principally associated with damage to the hippocampus and adjacent areas of the MTL (Milner, 1966) but can also arise from damage to other regions comprising the Papez circuit (see Aggleton and Pearce, 2001 for review). Firstly, it was shown that despite amnesiacs being severely impaired in their ability to describe or recognise prior events, they still exhibited normal or near normal facilitations of performance on tasks such as mirror tracing (Milner, 1962) where past events influence performance without requiring access to conscious processing. Furthermore, such patients may exhibit normal priming effects, where behaviour (such as reaction time) is influenced by prior exposure to stimuli in the absence of awareness (Warrington and Weiskrantz, 1968). Such findings led Cohen and Squire (1980) to suggest that LTM could be broadly divided into 'declarative' and

'procedural' systems (see Squire and Morgan, 1991 for a development of this view). A similar distinction between 'explicit' and 'implicit' memory was proposed by Graf and Schacter (1985), roughly corresponding to declarative and procedural systems respectively. These two systems were distinguished primarily as conscious awareness of a retrieved memory (explicit/declarative) vs. mnemonic influence on behaviour without the necessity for conscious awareness. Additionally, the products of declarative retrieval are used flexibly, they may be used to influence behaviour or not, whilst procedural memory automatically influences behaviour. Within these broad systems are further subdivisions into specialised memory stores characterised in terms of their specific attributes, for example explicit memory is subdivided into semantic memory, for facts and knowledge, versus episodic memory for unique prior events (see Schacter and Tulving, 1994; Squire and Zola, 1996 for reviews).

A model of memory incorporating greater fractionation was proposed by Tulving (1983, 1985, 1993). His view was that memory is fractionated into a larger number of categories such as episodic memory (memory for prior events), semantic memory (for facts), procedural memory (skills and habits; classical conditioning), short-term memory and a perceptual representation system, which underlies priming effects. Whilst the models discussed above have a number of similarities, there are some conflicts of opinion as to which components of each model correspond and the precise definitions of particular memory components. One example of a taxonomy of memory systems is shown in fig 1.1.

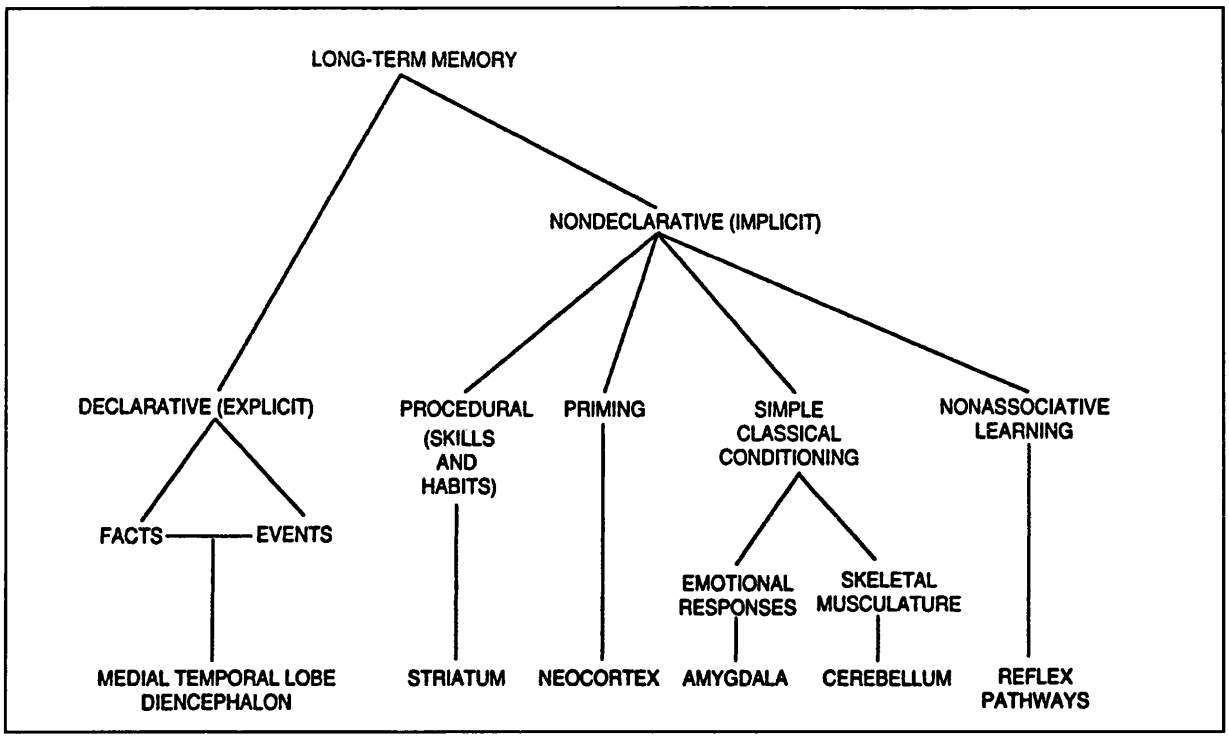

Fig 1.1 A taxonomy of memory systems (after Squire and Zola, 1996)

In addition to debates about the subdivision of processes within the memory system, there are questions as to the neural structures underlying each system, which often correspond with the features of one particular model. For example, Squire and his colleagues view semantic and episodic systems as parallel systems of declarative memory which are differentiated only according to the type of information being processed. They are thus believed to be anatomically co-localised within MTL structures in particular. By contrast, Tulving views episodic and semantic memory as being parallel but discrete systems, which are partially independent. Specifically, it has been proposed that the properties of declarative memory are those common to episodic and semantic memory, while episodic memory possesses additional, unique qualities (see Tulving and Markowitsch, 1998). For example, Tulving considers episodic memory to be 'autonoetic', involving the ability to mentally time-travel back

to the remembered episode, a feature marking it as phenomenologically distinct from semantic memory (see also Tulving, 2002).

Tulving suggests that encoding of declarative forms of memory occurs in a serial manner, with semantic encoding occurring prior to episodic. This predicts that damage to structures underlying encoding may result in equivalent impairments in both episodic and semantic memory, or greater impairments in episodic memory, but encoding deficits in semantic memory cannot occur in association with less marked episodic deficits. In contrast, retrieval is taken to be parallel and independent, such that double dissociations may occur (i.e. patients may exhibit equivalent deficits in episodic and semantic retrieval, or be more impaired in either form of memory). This assumption leads to the prediction of differing anatomical substrates supporting the retrieval of episodic and semantic memory, which the model of Squire and colleagues does not.

These models generate different predictions as to the nature of dissociations predicted on the basis of neurological damage, and thus a large number of neuropsychological studies of memory have focussed on these areas (see Squire and Knowlton, 2000; Markowitsch, 2000 for reviews).

The Neuroanatomical Basis of Episodic Memory

The neural processes supporting the encoding, consolidation and retrieval of memory can be considered as occurring in a sequence of different stages (see Markowitsch, 2000). The first stage comprises the transmission of sensory information to the cortex via sensory receptors. This information may then be transiently processed in working memory, mediated by posterior association cortex (Shallice and Warrington, 1970)

and prefrontal regions (see Courtney et al, 1998). However, such processing is not necessary for episodic encoding, as patients with severe working memory deficits may exhibit normal performance on episodic memory tasks (Shallice and Warrington, 1970). Information is then transferred into long-term memory, and a memory trace, or engram, is formed (Thompson, 1976; Craik, 1983). This encoded trace is then consolidated allowing maintenance of the trace over time (see Baddeley, 1997). The final stage is the retrieval of information, which can be considered as consisting of 'pre-retrieval' processes, engaged to actually retrieve a trace from memory, and 'post-retrieval' processing of the products of a retrieval attempt, such as evaluating the significance of the retrieved information in relation to current task demands (see Rugg and Wilding, 2000).

The transfer of information into LTM is most probably mediated by the structures of the 'limbic system' (Papez, 1937), comprising medial temporal cortex and diencephalic structures (including the amygdala, hippocampus and medial thalamic nuclei; see Markowitsch, 2000; Aggleton and Brown, 1999). The formation of memories from this input is widely believed to be mediated by synchronous firing of neighbouring synapses, resulting in physiological changes which increase the degree of functionally connectivity between these synapses (Hebb, 1949; see also Kolb and Whishaw, 1980).

The hippocampus has received a great deal of attention as the locus of such a Hebbian mechanism (e.g. Grasby et al, 1993; Hasselmo et al, 1996; Rempel-Clower et al, 1996; Schacter et al, 1996; Rugg et al, 1997; Reed and Squire, 1997; Vargha-Khadem et al, 1997; Eldridge et al, 2000), and experimentally-induced electrical activity can lead to neurophysiological changes in hippocampal slice preparations (Bliss and Lomo, 1973; Bliss and Gardner-Medwin, 1973; Eccles, 1986; Bliss and Collingridge, 1993). These

studies found that concurrent induction of activity in pre- and post-synaptic neurons resulted in increases in the influence of the pre-synaptic on the post-synaptic neuron. This effect persisted over considerable periods of time, and was named long-term potentiation (LTP; Bliss and Lomo, 1973). It was also found later that long term decreases in synaptic connectivity (long term depression; LTD) could be induced in hippocampal slice preparations, for example by low frequency stimulation protocols (see Debanne and Thompson, 1996 for review). These studies, together with other studies of learning-induced changes *in vivo* (particularly in *Aplysia*; e.g. Castelluci et al, 1978; see also Kandel, 1989) have suggested that such changes rely upon the concentration of Ca^{2+} ions within post-synaptic cells, determined principally by its entry through glutamate receptors, specifically the NMDA (N-methyl-D-aspartate) subtype. These channels are normally blocked by Mg^{2+} ions, even when ligands are bound, but this can be displaced by depolarisation of the post-synaptic cell, achieved through glutamate binding to AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid) receptors, which are ligand gated Na^{+} channels. Initial connectivity changes are mediated by increased release of glutamate from pre-synaptic vesicles (mediated by retrograde messengers from the post-synaptic cell, probably NO (Schuman and Madison, 1991) and increased sensitivity of AMPA receptors, both of which lead to increased connectivity between pre- and post-synaptic cells. Memory is then consolidated by activation of a molecular cascade (see Bailey et al, 1996 for review) which results in increased synthesis of AMPA receptors and changes in the morphology of dendritic spines, leading to longer term changes in connectivity. As depolarisation of the post-synaptic cell requires multiple pre-synaptic inputs, and the changes in connectivity are specific to those synapses active at the time of depolarisation, the various pre-synaptic cells become associated with one another.

However, whilst the hippocampus is a good candidate region for memory formation, the degree to which different types of memory depend upon it is not clear. One view is that the hippocampus and surrounding MTL regions (entorhinal, perirhinal and parahippocampal cortices), collectively known as the 'hippocampal system' act as an integrated assembly for encoding of both episodic and semantic memory (Zola-Morgan et al, 1989; Squire and Zola-Morgan, 1991; see Squire and Knowlton, 2000; Aggleton and Brown, 1999). An alternative view, based on findings that focal hippocampal pathology early in life leads to pronounced impairments in episodic memory with relative sparing of semantic knowledge, is that episodic and semantic components of memory are at least partly dissociable, with the hippocampus only crucial for episodic memory (Vargha-Khadem et al, 1997).

The role of the hippocampus in memory retrieval is not so clear. Hippocampal damage leads to profound anterograde amnesia (amnesia for events subsequent to the damage) with retrograde amnesia (memory for events prior to hippocampal damage) being more limited – very recent events are not remembered, but the amount of time over which retrograde amnesia extends seems to depend on the extent of damage to surrounding MTL structures (see Squire and Zola, 1996). There is considerable debate in the literature as to whether this amnesia is temporally graded (e.g. Rempel-Clower et al, 1996; Reed and Squire, 1998; Rosenbaum et al, 2001; Cippolotti et al, 2001). The ability to retrieve distant memories has led to proposals that the hippocampus does not act as the permanent store for episodic memories, but that it initially acts to link disparate neocortical sites, particularly in association cortices, which slowly become associated with one another such that the memories become independent of the hippocampus (see Marr, 1971; Eichenbaum, 1997; Knowlton and Faneslow, 1998).

However, Moscovitch and colleages (Nadel and Moscovitch, 1997; 1998; Viskontas et al, 2000) argue that remote episodic memories are not always spared in MTL amnesia, and that damage or dysfunction can result in extensive retrograde amnesia for personal episodic memories. Evidence in favour of a role for the hippocampus in retrieval comes from the findings that disrupting MTL activity pharmacologically (Liang et al, 1994; Riedel et al, 1999) or electrically (Halgren et al, 1985) severely impairs retrieval processes. Moscovitch and colleagues have proposed that the hippocampus is necessary for retrieval of episodes within a spatio-temporal framework or context, regardless of the age of memories. One notable characteristic of patients with retrograde amnesia is that their descriptions of past events tend to be less detailed than those of controls, and may be dependent on semantic knowledge about the relevant period of their lives, rather than genuine episodic retrieval (see Nadel and Moscovitch, 2001). If indeed episodic memory were shown not to exhibit truly graded retrograde amnesia, in contrast to semantic memory (e.g. Verfaellie et al, 1995), it would provide further evidence for dissociable neural substrates for these forms of memory, but the issue remains contentious, and the full range of arguments is beyond the scope of the present review.

Damage to a number of regions outside the Papez circuit can also disrupt memory encoding and retrieval, but the deficits reported appear to be more related to strategic processes rather than retrieval *per se*. For example, left and right prefrontal cortex (PFC) are believed to subserve organisation of information during encoding or retrieval, and appear to have functionally distinct roles in the strategic control of memory (e.g. Rapczak et al, 2001). Further understanding of the brain regions involved in memory encoding and retrieval processes has been gained from functional imaging studies of these processes. A considerable number of these studies use event-

related designs, which require signals to be time-locked to events of experimental interest (see chapter 3). Thus, some of the most commonly employed paradigms for imaging of retrieval processing are based on recognition memory, which is the ability to discriminate between presented items on the basis of whether they have been studied previously. It is important to understand theories as to how people make recognition judgements before we discuss the findings from such studies.

Theories of Recognition Memory

A key issue in understanding how performance on recognition tasks, and the neural correlates of recognition memory, relate to our understanding of episodic memory regards the nature of the processes underlying recognition judgements. There has been considerable debate as to whether recognition depends on multiple processes (e.g. Atkinson and Juola, 1974; Huppert and Piercy, 1976; Mandler, 1980; Jacoby and Dallas, 1981; Tulving, 1985; Yonelinas, 1994) or is better characterised as being due to a single process (e.g. Murdock and Dufty, 1972; Murdock, 1982; Hintzman, 1986).

Single process models suggest that recognition can be well modelled by signal detection theory, that is the ability to extract a signal from background noise based upon relative strength and setting of a response criterion. In the case of recognition, this strength is based upon relative familiarity, with 'old' and 'new' items modelled as two overlapping normal distributions, with means separated by a parameter, d', which can be related to recognition accuracy. In contrast, dual process models assume that recognition performance receives contributions from both 'familiarity', the feeling that a stimulus has been previously encountered but without explicit recall of the event itself, and from 'recollection', the re-experience of the encoding event,

including both the stimulus and context. This is an important issue as some authors consider such re-experience to be an essential feature of episodic memory (e.g. Tulving, 1983; Tulving, 2002). We shall discuss some of the evidence supporting dual process models, and how familiarity and recollection processes might be dissociated, in order to interpret functional and anatomical findings from recognition studies (for more in-depth discussion see Yonelinas, 2001).

One method of investigating recognition memory is to plot the receiver operating characteristic (ROC), that is the function relating the number of hits and false alarms subjects make on a recognition task. This is manipulated by varying levels of response confidence, as when the criterion for defining objects as old is lax one predicts higher hits and false alarms than when the criterion is strict. The particular shape of this ROC function has implications for the models discussed above. The simplest signal detection models predict a ROC which is curvilinear and symmetrical along the diagnol (assuming that familiarity distributions for new and old items are Gaussian and of equal variance). However, with some early exceptions (e.g. Murdock and Dufty, 1972), ROCs have typically been found to be curvilinear and asymmetrical, with the proportion of hits at very low false alarm rates being higher than those predicted by the simple signal detection model. Signal detection models can still account for such asymmetrical patterns if the familiarity distribution for old items has greater variance than that for new items, but only if the degree of asymmetry is either constant or directly related to accuracy. However, ROCs with these features are not typical, and recognition accuracy and degree of ROC asymmetry are functionally independent (Yonelinas, 1994; Glazner et al, 1999). Dual process theorists explain this as the superposition of familiarity, modelled by a symmetrical signal-detection

type function and recollection, which provides an independent contribution to hits and thus results in an asymmetry which cannot be explained in terms of a single process.

Several methods have been developed trying to dissociate these proposed familiarity and recollection processes. One such method is the remember/know (R/K) procedure, where subjects, when a test item is attributed as old respond as to whether they 'remember' (R) specifically seeing the item, or whether they 'know'(K) the item was presented previously but cannot specifically recollect the presentation (Tulving, 1985). R responses are assumed to reflect recollection, and K responses reflect familiarity. However, since familiarity processes may also be active when recollection occurs this needs to be taken into account when estimating familiarity and recollection in these paradigms. The independence remember/know procedure, which assumes that recollection and familiarity are functionally independent (Yonelinas and Jacoy, 1995) calculates:

'remember' = R

'know' = F(1-R) hence F = know/(1-R)

These estimates model the shape of ROC curves well, supporting the concept of independent processes contributing to recognition, and that these processes are associated with different subjective experiences at retrieval. Other methods have also been used in an attempt to dissociate these processes. One approach is to identify conditions under which performance is dependent primarily on one or other process, and to examine dissociations in performance on standard recognition tasks with those reliant more heavily on recollection or familiarity in order to infer the contributions of each process.

An example of this approach is based upon the assumption that recollection allows retrieval of qualitative information about an event such as the context (e.g. spatial position) or feature (e.g. colour) of a test item, or association with another item. Therefore associative recognition judgements, which should be dependent on recollection, can be used to probe episodic retrieval. Another method, introduced by Jacoby (1991), with similar assumptions to those above, is to compare performance on 'inclusion' and 'exclusion' tasks. During encoding stimuli differ as to some feature or context, such as whether they are presented at the top or bottom of a screen, or whether they were presented in the first or second of two lists. Recognition tasks then take two forms – in the inclusion condition subjects perform a simple recognition task where all old items are 'targets', whilst in the exclusion condition subjects are instructed to respond only to targets from a particular condition e.g. only items presented at the top of a screen. It is assumed that performance in the inclusion condition relies on both recollection and familiarity, while the extent to which each is used in the exclusion task can be calculated according to the number of items from the non-target condition mistakenly attributed as targets:

Probability of a hit in inclusion condition $p(\text{Inclusion}) = R + (1-R)F$

Probability of incorrect response to non-target in exclusion $p(\text{Exclusion}) = (1-R)F$

Therefore: $R = P(\text{Inclusion}) - P(\text{Exclusion})$

$$F = P(\text{Exclusion})/(1-R)$$

Another assumption of many dual-process models is that completion of familiarity processing occurs before recollection is completed, such that manipulation of response times (either by setting a short response deadline within the experiment, or by separating results according to reaction times (RTs)) can be used to infer the

contributions of familiarity and recollection (e.g. Atkinson and Juola, 1974; Jacoby, 1991; Mandler, 1991; Hintzman and Curran, 1994). Division of attention during retrieval has been another manipulation used, as most models assume recollection to be a conscious, effortful process which should be disrupted by division of attention, whilst familiarity is considered more automatic and is thought to be less disrupted by divided attention manipulations (e.g. Gruppuso et al, 1997; Dodson and Johnson, 1996). An alternative to examining effects within a task is to compare the results of manipulations across different types of task. Recollection is thought to engage some of the same processes as free recall (with both relying on retrieval of episodic memory) so a popular approach has been to manipulate the same factors in tests of free recall and recognition, under the assumption that those disrupting free recall to a greater extent than recognition probably influence recognition primarily by disrupting recollection (e.g. Craik et al, 1996; Anderson et al, 1998). However, such an interpretation is complicated by the fact that recollection and free recall are not identical – for example, retrieval processes in recognition tasks have greater 'environmental support' (see e.g. Mangels et al, 2002).

Each of the techniques described above for dissociating recollection and familiarity has various advantages and disadvantages, and makes differing assumptions. Findings which are not consistent across different types of studies may reflect artefacts due to aspects of particular procedures, but findings consistent across them are more likely to be valid, and we will review these briefly here. A number of manipulations at encoding result in dissociable effects on familiarity and recollection during subsequent recognition. Manipulating the 'level of processing' modulates both recollection and familiarity processing, but to different degrees. 'Deep' processing, such as making judgements about the meaning of a stimulus, results in improved

levels of recognition compared to 'shallow' processing of simple perceptual aspects of stimuli (Asthana and Nagrani, 1984). Various studies, using a variety of paradigms (e.g. Toth, 1996; Gardiner et al, 1999; Yonelinas, 2001) have generally shown that both recollection and familiarity are increased by deep processing, but that the effect is greater on recollection. Increasing the amount of time available for the study of each item (particularly if this takes the form of repeated, distributed presentations of each item rather than a single lengthy presentation) increases familiarity and recollection to a comparable degree (e.g. Jacoby et al, 1998, 1999; Yonelinas et al, 1996), whilst increasing the number of study items decreases recollection, but does not appear to affect familiarity (Yonelinas, 1994). These findings suggest that the chance of items being recollected is particularly dependent on effortful processing, which may limit the number of items which can be encoded into episodic memory within a particular period of time.

At test, restricting the time available for response selection results in recognition deficits generally, which are particularly severe for recollection. Studies manipulating response deadlines in simple and associative recognition tasks show that recognition accuracy for items improves above chance level at shorter deadlines than accuracy of memory for associative information (e.g. Hintzman and Curran, 1994; Johnson et al, 1994). Exclusion tasks with increasing response deadlines show that at shorter deadlines, non-targets are mistakenly accepted as targets, and then rejected at longer deadlines. This has been interpreted as showing that old/new discrimination can be made on the basis of familiarity alone at low response deadlines, with recollection used to reject non-targets at longer deadlines (e.g. Hintzman et al, 1998; Jacoby, 1999). Changing the perceptual characteristics of items between study and test, such as size or colour decreases recognition performance. The effect appears to be specific

to familiarity when test items are words (e.g. Toth, 1996; Rajaram, 1993), with recollection unaffected, but other studies using objects such as geometric shapes have found decreases in both recollection and familiarity (e.g. Yonelinas and Jacoby, 1995). Modulating the fluency of processing, such as by presenting certain items more clearly than others, or by revealing words letter by letter ('revelation effects'), results in improved recognition (e.g. Whittlesea et al, 1990; Whittlesea and Williams, 2000). Such manipulations can also be used to increase false alarm rates. These effects have been found not to increase estimates of recollection, but to increase false alarms due to familiarity processing (e.g. LeCompte, 1995) and it is notable that normal revelation effects are seen in temporal lobe amnesics (Verfaellie and Cermak, 1999). One more consistent finding is that use of new items which are semantically related to old items increases false alarm rates considerably. Normally false alarms are principally due to familiarity errors, but semantically related lures lead to significant increases in false recollection rates (e.g. Israel and Schacter, 1997; Mintzer and Griffiths, 2000).

This review is not comprehensive (for more in-depth coverage see Yonelinas, 2001) but covers the main findings which are reasonably consistent across studies and dissociation techniques. It suggests that recognition can be well modelled as two processes: familiarity, a relatively rapid discrimination of old and new items which is not accompanied by contextual details, may be relatively automatic and is tied to perceptual and semantic characteristics of test items. Recollection is a slower, more effortful process which is accompanied by conscious experience of remembering the encoding episode, together with contextual details. There is also evidence for different neural correlates of these processes underlying recognition, and we will finish this chapter with a review of this evidence.

The Neural Basis of Recognition Memory

Various methods can be used to examine the neural basis of cognitive processes. Studies of brain damage, both in human patients and animal models provide strong evidence as to the necessity of a brain structure for performance on a particular task, but do not prove that all underlying processes are subserved by these structures. In contrast, functional imaging studies reveal neural activity which is correlated with particular processes, but cannot prove that such activity is necessary for task performance. As we have previously discussed the neuropsychological evidence for the neural basis of episodic memory, which is pertinent to that supporting recognition memory, we will give a brief discussion of where differences in recollection and familiarity have or have not been found.

A number of studies have found that when damage is relatively selective for the hippocampal formation or the fornix (the structure connecting the hippocampus to the mamilliary bodies and anterior thalamic nuclei) that recall is impaired to a greater degree than recognition, implying that these areas may be crucial for recollection but not familiarity (see Spiers et al, 2001 for review; but see Stark and Squire 2001; 2003 for contradictory evidence). Amnesics are more impaired on tests of associative vs. simple item recognition (e.g. Mayes et al, 2001) and tend to misattribute frequently presented items as having been presented recently and vice-versa (Mayes et al, 1989). This suggests that they may be making such judgements based upon familiarity, with the errors above predicted by a signal detection account. These findings suggest that familiarity is disrupted to a lesser extent than recollection in amnesics (Yonelinas et al, 1996) though other studies have not found selective deficits (e.g. Knowlton and Squire, 1995). It has been shown that amnesic patients may show more pronounced

deficits in associative memory (e.g. Kroll et al, 1996; Mayes et al, 2001; Vargha-Khadem et al, 1997), particularly when the types of information are processed by different cortical regions e.g. face-voice vs. face-face associations. Such findings have been taken to imply that hippocampus is critical for binding together associations from different cortical modules, consistent with a number of computational models of its function (e.g. Marr, 1971).

In contrast to the findings supporting a privileged role for the hippocampus in associative processing, other studies have found equivalent deficits in associative and single item recognition in patients with hippocampal damage. For example, Stark and Squire (2003) presented a series of word pairs in a continuous recognition task, similar to that employed by Kroll et al (1996). Some trials involved presentation of entirely novel word pairs, others exact repeats of previous pairings, whilst other trials contained one old and one new word, or two old words in a novel pairing. Only exact repeats were targets, and failure to reject familiar words in novel pairings would be predicted if associative memory were impaired to a greater degree than memory for single items. However, Stark and Squire found equivalent deficits in all conditions, contradicting the associative/item distinction proposed. Similar results were obtained in the same experiment using syllable pairs combined into words or non-words, and pairs of faces and houses. However, it is worth noting firstly that all the associative tasks required within-modality associations (all were visual, and each task only employed either verbal or non-verbal stimuli) whereas between-modality associations may be more affected by MTL damage. Secondly, the patients showed some extra-hippocampal pathology, largely parahippocampal, and while the apparent distribution of damage varied between patients, leading the authors to suggest that all effects seen

were due to hippocampal damage, it may be that this parahippocampal damage is primarily responsible for the item recognition deficits seen.

The interpretation above is supported by the findings from developmental amnesia, which suggest that bilateral hippocampal damage need not be associated with deficits in recognition, and is much more disruptive of episodic than semantic memory (Vargha-Khadem et al, 1997; Baddeley et al, 2001). On the one hand, developmental amnesia may be considered an ideal model for hippocampal damage, with well circumscribed lesions and sufficiently early anterograde amnesia to make determining acquisition of new memory less complex. Alternatively, such cases may be regarded as showing exceptions to general rules, with the capacity for functional reorganisation and/or development of compensatory strategies in the developing brain leading to a different pattern of deficits to those seen in equivalent cases with adult-onset (see Squire et al, 2004).

Other amnesic patients have been examined on recognition memory tasks using the R/K procedure. The findings from these studies do not present a clear picture, with two reporting reduced proportions of R judgements in patients with hippocampal damage (Holdstock et al, 2002; Yonelinas et al, 2002) while another study found that comparing patient results with those for normal subjects after a one week study-test delay period (in order to roughly equate overall performance) showed equivalent effects on estimates of recollection and familiarity (Manns et al, 2003). The interpretational problems arising from subjectivity in making R/K judgements (see Donaldson, 1996) are increased for between-group comparisons, as potential response bias is very difficult to control for, and differences in the strategies employed by patients and controls may lead to conflicting and misleading results.

The findings above fail to present a consensus as to the exact role of differing structures in recognition memory. However, two general points come through – firstly that damage to the hippocampal system may be associated either greater deficits in recollection and associative memory than familiarity and object memory, or impairments may be equivalent. Secondly, increasing the size of MTL lesions increases the severity of the deficits observed. On balance, this suggests that the hippocampus is more important for recollection than familiarity and for retrieval of cross-modality associative information than simple item memory, though the nature of any relation between the phenomenological experience of recollection and retrieval of associative information is not proven. Familiarity is likely supported by adjacent cortical areas (see Brown and Aggleton, 2001; Rugg and Yonelinas, 2003). It may be moderately impaired in patients with hippocampal damage due to hidden pathology, excitotoxic effects in parahippocampal regions as a result of hippocampal/fornix damage (see Mumby et al, 1996 for a demonstration of this in rodents) or due to loss of support from episodic memory processes. However, it would not be predicted that familiarity would ever show greater impairments than recollection following hippocampal damage.

All the studies discussed above employed patients with bilateral damage. Patients with unilateral damage, such as those who have undergone unilateral temporal lobectomy to treat intractable epilepsy, show much more subtle memory deficits. Various authors have proposed differing roles for left and right temporal lobes in memory processing, such as specialisation for verbal (left) vs. visuo-spatial information (right) (e.g. O'Keefe and Nadel, 1978), or for recollection (left) vs. familiarity (right) (Blaxton and Theodore, 1997), although the latter findings may reflect criterion shifts or response bias in the R/K paradigm. In any case, unilateral

temporal lobe damage does not appear to fully disrupt any form of recognition memory.

Frontal lobe damage also impairs performance on memory tests, although deficits are typically less severe than in patients with MTL damage. Free recall is typically disrupted to a greater degree than is recognition, and recognition tests generally show greater impairments in source and associative memory than item memory. These memory deficits have been observed even in patients with preserved semantic knowledge (e.g. Janowsky et al, 1989). Neuropsychological studies suggest that damage to frontal lobes, particularly dorsolateral prefrontal cortex (DLPFC) results in particularly marked associative recognition deficits (Kopelman et al, 1997), indicating that this region is more crucial for recollection than familiarity processing.

The role of processes subserved by prefrontal cortex (PFC) in memory processing is less clear than those subserved by MTL. Whilst MTL may be the locus of a Hebbian associative process, PFC is associated with organisation of cortical modules and temporal ordering, and at least some aspects of the memory deficits may be due to poor encoding strategies. Use of organisational strategies and list organisation tend to be lower in patients with damage to PFC (Gershberg and Shimamura, 1995; Mangels, 1997) and instructing patients to use particular semantic strategies can ameliorate memory deficits (Mangels, 1997). Some patients also show excessively high false alarm rates, implying a further role for PFC at retrieval in directing appropriate behavioural responses to retrieved information. Such a role at retrieval is supported by the finding that giving strategic instructions during test may reduce recall deficits (Gershberg and Shimamura, 1995). Therefore PFC may have an important role in the strategic regulation of both encoding and retrieval. As mentioned above, however, neuropsychological studies give only limited insights into the neural correlates of

recognition memory, and we will now consider functional imaging findings, concentrating on the event-related potential (ERP) and functional magnetic resonance imaging (fMRI) correlates of recognition memory.

ERP Correlates of Recognition Memory

Recording and averaging scalp EEG time-locked to an event of interest is one method of correlating neural activity with cognitive processes (for more detail see chapter 3). Studies of recognition have most typically examined differences in the ERPs associated with correctly classified old and new items from either a study-test or continuous recognition paradigm, and characterised these effects in terms of their timing and scalp distribution. Comparisons are chosen so as to isolate particular processes – for example activity elicited by correctly classified old and new test items should reflect equivalent processing of retrieval attempt and successful classification, but new items should be associated with minimal successful retrieval of episodic information and this should be reflected in ERP differences. It is important that cue types are equivalent in order to interpret any such differences unequivocally (see chapter 3).

Contrasts of ERPs elicited by correctly classified old vs. new items during recognition tests consistently show a positive amplitude shift in the ERP associated with old items. This shift appears to comprise at least three temporally and topographically distinct 'old/new' effects. The most well established of these effects is a positivity typically onsetting between 300 and 500ms with a duration of ca. 500ms, maximal at left parietal electrodes (Johnson et al, 1985; Wilding et al, 1995; Wilding and Rugg, 1996; Rugg et al, 1997b). This 'left parietal old/new' effect has been proposed to be an ERP

correlate of recollection (discussed further below). A second effect, less consistently elicited than that over left parietal scalp, is evident as an early (ca. 300-500ms) bilateral shift over the frontal electrodes. This effect is not modulated by depth of processing manipulations, and has been proposed by some authors as an ERP correlate of familiarity (Rugg et al, 1998; Curran, 2000). A third, late-onsetting (ca. 600-800ms) old/new effect shows a right frontal distribution, and has been proposed to reflect post-retrieval processes operating on the products of retrieval (e.g. Wilding and Rugg, 1996). The scalp distributions of these three effects are illustrated in figure 1.2.

The Left Parietal Old/New Effect

To establish the relevance of the left parietal effect to retrieval of episodic memory it is important to establish firstly that this effect does indeed reflect differences due to the processing of old and new items. Alternatively it might reflect modulation of temporally and topographically overlapping ERP components which are sensitive to other factors which may be different for old and new items in typical recognition tasks, but need not be so. Secondly it needs to be established that it reflects episodic retrieval rather than other processes, such as familiarity, which may support performance on recognition tasks.

Soon after the identification of old/new effects, a number of differences between old and new items in standard recognition tasks were highlighted, such as target/non-target effects, confidence, response latency, stimulus probability and implicit memory effects (e.g. priming) (see Karis et al, 1984; Neville et al, 1986). It was suggested that such factors might modulate ERP 'components', which are positive and negative

deflections in a typical ERP waveform with particular spatial and temporal distributions (see chapter 3 for further discussion). In particular it was proposed that the factors listed above might influence the P300 and N400 components (a positive shift onsetting at around 300ms post-stimulus and a negative shift onsetting at around 400ms post-stimulus, respectively), resulting in ERP differences which did not truly reflect memory processing.

The P300 has been shown to be sensitive to target effects and to stimulus probability (see Donchin and Coles, 1988) and so one view was that these factors might result in P300 modulations resulting in the observed left parietal effects. However, left parietal old/new effects have been shown not to interact with stimulus probability (Friedman, 1990; Herron et al, 2003), and to be sensitive to retrieval but not to target effects in an oddball paradigm (Smith and Guster, 1993). Additionally, it was shown by Rugg and colleagues (1992), by dissociating repetition of items and response requirements, that word repetition effects could not be solely attributed to facilitated response processing of old items. Therefore P300 modulations do not appear to account for left parietal old/new effects.

However, early (ca. 300-500ms) old/new effects do appear to share sensitivities with the N400 component. For example, both are sensitive to repetition of words but not non-word letter strings (Rugg and Nagy, 1987) and can be eliminated by increasing the temporal distance between repeated items (Rugg and Nagy, 1989; Karayandis et al, 1991). In contrast, later effects over left parietal scalp (500ms+) are not sensitive to such manipulations. These findings, as well as the differences in scalp distribution (effects with different scalp distributions are taken to reflect engagement of different

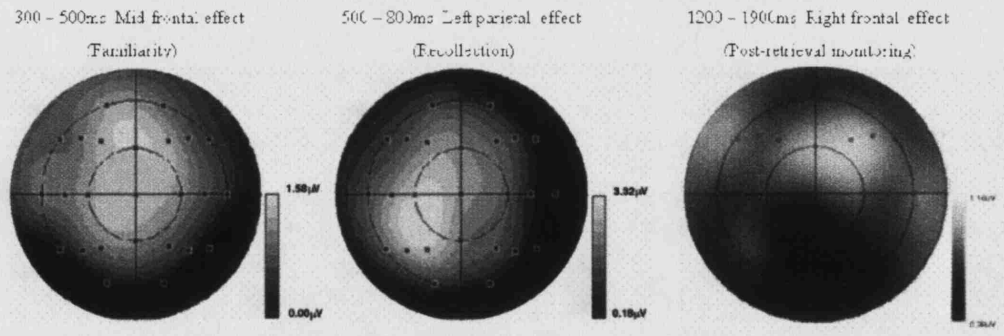

Figure 1.2 Topographic maps showing the scalp distribution of old/new effects, and the processes with which they have been proposed to correlate by Rugg and colleagues (Adapted from Allan et al, 1998 and Rugg et al, 1998)

neural populations and hence cognitive processes – see chapter 3a for further discussion) strongly suggests that the left parietal old/new effect is functionally, temporally and topographically distinct from P300 and N400 components (see Johnson, 1995). Hence the left parietal effect can be considered a genuine old/new effect, though it remains possible that old/new differences not supporting or contingent upon episodic retrieval might elicit this effect (see Rugg and Wilding, 2000).

Early studies of old/new effects conceptualised them as reflecting a single retrieval related (or, in some cases, specifically word repetition) effect. However, as discussed previously, recognition memory can be considered as being supported by at least two phenomenologically, and arguably neurophysiologically, distinct processes of familiarity and recollection. A number of studies have addressed whether old/new effects can be separated according to whether particular items were recognised on the basis of familiarity or recollection. In addition to demonstrating potential indices of these processes, such experiments also contributed to the single vs. dual-process

debate in recognition memory – if old/new effects elicited by recollection and familiarity were associated with qualitatively distinct scalp distribution this would provide evidence for different neurophysiological, and hence cognitive, bases for the two processes lending support to dual-processing theories. If, however, old/new effects were shown to differ only in magnitude then this would provide some support to single-process models, although such findings could not rule out differential engagement of structures not making significant contributions to electrical activity at the scalp (see chapter 3a).

Early experiments provided apparently conflicting evidence regarding the significance of the left parietal effect. Smith and Halgren (1989) reported that the effect was absent in patients with left unilateral temporal lobectomies, and interpreted this as evidence for a correlation between the left parietal effect and episodic retrieval (recollection), given the proposed role of temporal lobe in memory (see earlier). However, this assumes a selective effect of the lesion on recollection which is unlikely to be completely accurate (see above). Another study by Potter and colleagues (1992) found that administration of the anticholinergic drug scopolamine both disrupted recognition memory tasks and increased the magnitude of left parietal effects. They argued that disruption of cholinergic transmission would impair recollection, and that the increased magnitude of left parietal effects reflected increased familiarity processing to compensate. However, cholinergic receptors are widely distributed, and interfering with transmission may have impaired other processes supporting recognition memory, such as monitoring or strategic control.

A study by Smith (1993) compared ERPs to recognised old items according to whether they were 'remembered' or 'known' using a R/K paradigm (see earlier). He found that left parietal effects associated with R responses were larger than those

associated with K responses. However, it could be argued that such findings reflected differences in confidence, or the proportion of guesses in each category. Additionally it has been argued that the use of a single R/K/N judgement can result in adoption of a liberal response criterion, such that R/K attribution may reflect a quantitative rather than qualitative difference (see Hicks and Marsh, 1999). An alternative to using R/K judgements is to use a task which requires recollection of specific information to give an accurate response, such as by requiring source judgements. Here recollection can be operationalised as recognition accompanied by accurate source judgments, and familiarity as recognition accompanied by inaccurate source judgments. Such methods have an advantage over R/K paradigms in that the categorisation is less dependent on subjective judgements by the participants, although source judgements may not fully index recollection as some trials may be associated with retrieval of contextual details other than the source specified by the experimenter.

Rugg and colleagues (1995) examined recognition and source memory for high and low frequency words presented in two different contexts. They found that low frequency words were better recognised than high frequency words and were more likely to receive accurate source judgements. Such items elicited larger old/new effects, arguably reflecting increased levels of recollection. However, because the items forming the two classes of ERP differed this result is difficult to interpret unequivocally. Wilding and colleagues carried out two other studies of source memory directly contrasting ERPs elicited by accurate and inaccurate source judgements to equivalent test items (Wilding et al, 1995; Wilding and Rugg, 1996). They reported larger old/new effects over left parietal electrodes for source hit vs. miss trials, supporting the view that the left parietal effect indexes recollection. Further support for this view was provided by Donaldson and Rugg (1998) who

examined recognition of pairs of objects which were either the same as during study or rearranged. They argued that responses to 'same' pairs would rely upon recollection to a greater extent than would those to 'rearranged' pairs, which would be more likely to be recognised on the basis of familiarity. In keeping with this view, 'same' pairs elicited greater left parietal old/new effects.

Whilst the studies discussed above provided evidence that left parietal effects did indeed reflect good recognition memory, they did not show dissociations in the scalp topographies associated with recollection and familiarity. This might have been due to 'contamination' of the ERPs in the familiarity conditions by recollection processes, such as where subjects recollect aspects of the study context, but not those required for accurate source judgements, or that dissociations between recollective and familiarity processes occurred only in structures to which ERPs are insensitive (see earlier).

Later studies did however show dissociable scalp topographies associated with recollection and familiarity. Düzel and colleagues (1997) used an R/K paradigm and identified different scalp distributions of ERPs elicited by R and K trials between 300-1000ms. Interestingly these differences were seen for both old and new items receiving such judgements, implying that at least part of this effect reflected 'autonoetic' vs. 'noetic' remembering, even when recollections were false. Futher evidence for differences in scalp distribution for familiarity and recollection came from the findings of Rugg et al (1998), who compared old/new effects elicited during a recognition task for words which were studied under either deep or shallow encoding conditions. They reported two distinct old/new effects – one between 300-500ms over frontal sites which was equivalent for both shallowly and deeply studied words, and a second topographically distinct and prominent left parietal effect which

was present only for deeply processed items. It was suggested that this reflected the greater proportion of recollected trials in the deep condition, and thus provided evidence for distinct neural correlates of familiarity and recollection. However, as depth of processing may not act exclusively by modulating recollection (see Toth, 1996), this interpretation should be regarded as tentative.

Another study supporting the recollection/familiarity dissociation examined recognition of words where some of the new words were very similar to words seen at study (Curran, 2000). It was proposed that both old words and related lures would be differentiated from unrelated new words by familiarity, whilst recollection would be necessary to discriminate between the lures and old words. In line with the findings described above an early frontal effect was sensitive to relative familiarity of words, whilst the left parietal effect discriminated between old and related words. Similar findings have been reported using a range of different materials and lures (e.g. Nessler et al, 2001; Curran et al, 2002; Curran and Cleary, 2003). Curran (2004) reported the results of two experiments investigating the effects of attention at encoding on ERPs formed on the basis of either R/K or confidence judgements. He found that dividing attention had larger effects on estimates of recollection than familiarity, in line with previous work, and that ERPs to old items from the divided attention condition showed equivalent early frontal effects, but decreased left parietal effects relative to ERPs from the full attention condition. These differences mirrored those in contrasts between ERPs to R and K trials. In the second experiment high confidence hits elicited larger left parietal effects than did their neutral counterparts as predicted, but crucially there were no differences in the effect when comparing high and low confidence correct rejections, supporting the view that left parietal effects do not reflect a generic confidence-sensitive process.

Finally it is noteworthy that studies of amnesic patients have revealed old/new effects which differ from those elicited in normal subjects. Mecklinger and colleagues (1998) reported that a group of patients with memory problems arising from chronic hypoxia were shown to have decreased (or reversed) old/new effects compared to controls, despite equivalent P300 responses in an oddball task. Even more compelling are the findings of Düzel et al (2001) who examined old/new effects elicited in a recognition task by 'Jon', a patient with bilateral hippocampal damage from a young age, with relatively normal recognition memory (one of the patients described by Vargha-Khadem et al, 1997; see earlier). They reported that the left parietal effect was greatly reduced in Jon, while his early frontal familiarity effects showed similar magnitude and distribution to those of control subjects.

Together these findings support the idea of the left parietal effect reflecting cognitive processes associated with episodic retrieval. Additionally, it has been shown by Wilding (2000) that the magnitude of the left parietal effect may reflect the amount of information retrieved from memory, as operationalised by the number of source features correctly identified in a source memory test.

The Right Frontal Effect and Postretrieval Processing

A number of the studies discussed above found another topographically and temporally distinct old/new effect – a sustained, late-onsetting (ca. 800ms) positivity maximal over frontal scalp. This effect has been reported in a number of studies employing tasks with more complicated response requirements than simple yes/no recognition such as source memory tasks (e.g. Wilding and Rugg, 1996) or R/K tasks (e.g. Düzel et al, 1997). Most commonly these right frontal old/new effects have been

prominent in conditions associated with good episodic retrieval i.e. R judgements in R/K tasks or accurate source memory judgements. One common interpretation of this effect has been that it reflects processing of the products of episodic retrieval in order to guide such judgements, in line with post-retrieval monitoring theories of right dorsolateral prefrontal cortex on the basis of fMRI studies (discussed further below).

More recently, however, it has been found that right frontal effects can also be elicited in conditions where little or no recollection is likely to have occurred, when items are recognised at low rather than high levels of confidence (Rugg et al, 2000). Together with findings from fMRI studies of right DLPFC (discussed further below), these results have led to an alternative interpretation of the significance of the right frontal effect as reflecting engagement of processes which monitor the products of a retrieval attempt, which may be unsuccessful, and may then drive further retrieval attempts in an iterative manner if retrieved information is insufficient to meet the requirements of the task (see Rugg et al, 2002). In either cases it does seem apparent that the right frontal effect reflects some form of monitoring of retrieval processing allowing appropriate guidance of behaviour, in line with some views of right frontal function derived from neuropsychological studies (see Shallice and Burgess, 1996).

Haemodynamic Correlates of Recognition Memory

We will now consider the findings from PET and fMRI studies of recognition memory. While such studies lack the temporal resolution of ERPs, making it difficult to conclusively determine the temporal order of neural activity (although with event-related fMRI relatively long differences may be captured by using basis sets with HRFs shifted in time; see Henson et al, 2000; see also chapter 3) they have much

greater spatial resolution, and provide more homogenous sampling of neural activity in the brain. We will discuss studies using both blocked and event-related designs, though focussing on the latter due to difficulties separating effects due to retrieval processing itself from those related to a retrieval state in block designs.

Early efMRI studies of recognition failed to elicit clear patterns of old/new effects (Schacter et al, 1997; Buckner et al, 1998), in contrast to findings from ERP and blocked fMRI and PET studies. However, these studies employed long inter-trial intervals which may have encouraged additional processing not related to retrieval, and only had a small number of trials, reducing statistical power (see Josephs and Henson, 1999; Meizin et al, 2000). However, later studies employing more trials and shorter inter-trial intervals found a number of old/new effects, particularly in frontal and parietal regions (see Rugg et al, 2002). Here we will initially focus on the significance of parietal and frontal effects, and their relationship to ERP effects. We will then turn our attention to effects within MTL.

Parietal Cortex

The parietal cortex, particularly Brodmann Areas (BA) 39 and 40, is one of the most consistently reported areas in fMRI studies of recognition memory (e.g. Henson et al, 1999; Konishi et al, 2000; McDermott et al, 2000; Donaldson et al, 2001; Wheeler and Buckner, 2003; 2004). Such activity has been reported in studies of simple yes/no recognition and studies employing source memory, exclusion or R/K tasks.

A number of studies have suggested different sensitivities of lateral parietal cortex to aspects of memory. Wheeler and Buckner (2003) reported that activity in BA 40/39 was increased not only for correctly recognised old items (hits) compared to correctly

rejected new items, but was also increased for new items incorrectly ascribed as old (false alarms). This suggests that this region may be sensitive to the subjective perception that presented information has been previously experienced, or alternatively that parietal activity reflects target effects of some sort. The former possibility is supported by the findings of McDermott et al (2000) who examined fMRI responses during recognition of word pairs which were either the same as at study (targets), consisted of words seen at study which had been rearranged (rearranged non-targets) or were new. They reported that rearranged as well as target pairs elicited greater left parietal activity than new items.

Other findings have suggested that left parietal activity is specifically related to recollection rather than familiarity, similar to the left parietal old/new ERP effect discussed earlier. For example, using R/K paradigms, it has been reported that areas of left parietal cortex show greater responses to old items which are associated with a subjective feeling of remembering (Henson et al, 1999; Eldridge et al, 2000). Source memory findings have also suggested that left parietal cortex is sensitive to episodic retrieval (Cansino et al, 2002). However, it should be noted that, in addition to the area that Henson et al (1999) reported as being sensitive to recollection, another parietal region, more anterior and medial, showed equivalent responses on remember and know trials. Together, these findings suggest that parietal cortex may serve functionally distinct roles in recognition.

This issue has been explicitly addressed by Herron et al (2004) and Wheeler and Buckner (2004). Herron and colleagues examined recognition under conditions with varied ratios of old and new items, under the assumption that brain regions concerned with retrieval *per se* would show invariant responses to old and new items regardless of old/new ratios, whilst those areas showing old/new by old:new ratio interactions

reflect post-retrieval processes which are affected by the salience and 'targetness' of recognition cues. They found old/new effects in medial and inferior lateral parietal cortex which did not interact with ratio effects, while more superior left parietal cortex was sensitive to old:new ratio, implying different functional roles for these regions. Wheeler and Buckner (2004), using an R/K procedure, compared activity in different regions of left parietal cortex for R and K trials. They reported that one region of BA 40/39 was equally sensitive to both remember and know trials, whilst two other regions, one lateral and one posterior to the area showing equivalent sensitivity, were selectively responsive to remembering. They showed a region by sensitivity interaction, supporting the view that some areas of left parietal cortex reflect activity contingent upon episodic retrieval of information, whilst other areas respond to the old/new status of the item but do not discriminate recollective and familiarity processes.

While lateral parietal regions are most consistently reported in recognition tasks, other more medial regions are also engaged. Activation of the precuneus (BA 7/31) has been reported in blocked recall studies (e.g. Tulving et al, 1994; Shallice et al, 1994; Buckner et al, 1995; Schacter et al, 1996) and event-related recognition paradigms (e.g. Henson et al, 1999; Konishi et al, 2000; Wheeler and Buckner, 2003). This region is associated with visual imagery (e.g. Fletcher et al, 1995) and might reflect visual representation of prior episodes. Another nearby region reported in many studies of recognition is the posterior cingulate cortex (BA 29/31). As with inferior lateral parietal cortex, posterior cingulate has been associated specifically with recollection rather than familiarity (e.g. Henson et al, 1999; Wheeler and Buckner, 2004) and is insensitive to old:new ratio (Herron et al, 2004).

The exact roles of these different regions in retrieval in not clear, but inferior lateral parietal cortex, precuneus and posterior cingulate are candidate regions supporting a 'retrieval circuit' (see Nyberg et al, 2000; Herron et al, 2004), possibly specific to episodic retrieval. The inferior lateral parietal effects are also the likely haemodynamic correlates of the ERP left parietal effect. Other areas of parietal cortex may reflect other para-retrieval processes, such as control of attention or orientation in response to retrieval.

Prefrontal Cortex

Prefrontal regions have commonly been reported in both blocked and event-related studies of retrieval. In blocked studies of retrieval, prefrontal activations have been predominantly right lateralised, with both anterior PFC and DLPFC (BA 9,10,46) reported across a range of retrieval tasks (see Fletcher et al, 1997 for review). Activity has also been reported in a number of other prefrontal regions, both left and right (e.g. Kapur et al, 1995; Rugg et al, 1996), but these findings have been less consistent. Use of simple blocked designs makes interpretation of these different activations difficult. A number of studies have employed designs which allow distinctions to be made between activity reflecting retrieval success (i.e. actually dependent on retrieval of memory), versus that reflecting adoption of a retrieval mode (a cognitive state adopted during retrieval processing) or reflecting retrieval effort.

Studies attempting to resolve these possibilities have reported conflicting conclusions. Tulving et al (1994) examined rCBF changes associated with recognition for auditory sentences in test blocks containing either all new or all old items. Greater right PFC activation was evident for the old block, leading the authors to suggest that this effect

reflected retrieval success. However, given that each block contained only test items of one type, it is possible that subjects realised early in 'new' blocks that all items were novel and thus failed to engage in retrieval attempts. A subsequent study (Kapur et al, 1995) used blocks containing either 15% or 85% old items and contrasted these. Both high and low density blocks were associated with right frontal activity relative to a block where a semantic control task was performed, but there was no significant difference in this region reflecting the target density. This suggested that there was no effect of retrieval success. Another study using all old or all new items in a block (Nyberg et al, 1995) also found that recognition tasks activated right PFC relative to baseline, but no effect of retrieval success. This led to the conclusion that activity in this region may reflect adoption of a retrieval mode.

In contradiction of this view, Rugg and colleagues (1996) compared PET activity during recognition blocks containing zero, 20% or 80% old items. They found that both the 20% and 80% conditions showed prefrontal activation relative to the zero condition, suggesting sensitivity to retrieval success. Differences between the 80% and 20% conditions were present, but small and it was suggested that the relatively small increases with density reflected extended activity after each retrieved stimulus, decreasing the sensitivity to density effects due to potential interaction of overlapping haemodynamic responses (e.g. non-linear summation).

Event-related designs allow easier separation of task and item effects and efMRI studies have commonly reported frontal activity associated with correct recognition. These effects are often left-lateralised (particularly left anterior PFC, BA 9/10; see Rugg et al, 2002; Sakai, 2003) though a number of studies have also reported right prefrontal activity (e.g. Henson et al, 1999; 2000 ; Konishi et al, 2000). Notably, these frontal areas revealed in efMRI studies may show delayed responses relative to

responses from other brain regions, such as parietal cortex, and may be better revealed using a delayed HRF (e.g. Henson et al, 2000).

The left anterior prefrontal cortex has been shown to respond more strongly to trials attracting R than K judgements in R/K tasks (Henson et al, 1999; Wheeler and Buckner, 2004). A more inferior region than those reported in the studies above has been reported to respond to both correctly recognised old items and correctly rejected lures (where it is assumed that to correctly reject lure items the study episode must be recollected in order to oppose acceptance on the basis of familiarity) in a recognition task (McDermott et al, 2000). The possibility of dissociable roles for regions within left prefrontal cortex during retrieval of words was addressed by Dobbins et al (2002). They used a combination of recognition and source memory tasks, and hypothesised that left prefrontal cortex could support (at least) three distinct roles. Firstly, some effects might reflect access to or maintenance of lexical or phonological representations of cue words, and should be present during encoding and both retrieval tasks. Secondly, the semantic analysis of retrieval cues would be expected during both item and source retrieval, though it may be greater in the latter due to the potential usefulness of cue specification in source selection. Finally, some effects may operate post-retrieval to evaluate the products of retrieval and guide appropriate responses, and would be expected to be revealed primarily by the source retrieval task. Dobbins and colleagues concluded that left anterior inferior PFC is involved in controlling the retrieval of semantic information and cue specification, while a more posterior region appears to play a role in short term maintenance of lexical information. Frontopolar and left DLPFC were engaged only in the source task and are candidates for evaluative processes. Interestingly, responses in DLPFC were

equivalent for source hit and miss trials, suggesting that they are not contingent upon successful retrieval.

Henson and colleagues (2000) have suggested that different regions of right prefrontal cortex may have functionally discrete roles in retrieval. They reported that anterior and ventral regions of right PFC showed a similar pattern of responses to left anterior PFC, and may reflect retrieval success. In contrast, right dorsolateral PFC (DLPFC) was more active when hits were associated with low vs. high levels of confidence and similar areas have been reported in know vs. remember contrasts (Henson et al, 1999). These findings suggest that the role of right DLPFC cannot simply reflect retrieval success or amount of information retrieved. It has been proposed that activity in this region may reflect 'retrieval monitoring'. Such a process operates on the products of a retrieval attempt (successful or unsuccessful), guides responses and can iteratively drive further retrieval attempts if the products of prior attempts are insufficient to respond appropriately. By this account, when the amount of material retrieved is close to a subject's response threshold, a greater amount of monitoring is engaged than when it is far from such a threshold. For a recognition response, those items which are answered with low confidence are close to the response criterion and hence engage monitoring processes. Further support for a role of right DLFPC in post-retrieval monitoring comes from the study of Rugg et al (2003), who compared the haemodynamic correlates of recognition and exclusion tasks. Performance on the exclusion task depends on the ability to appropriately reject previously seen non-targets, which should require increased post-retrieval monitoring. Although some areas of right DLPFC showed old/new effects in both tasks, others showed enhanced effects during the exclusion task, supporting the monitoring hypothesis.

The monitoring interpretation of DLPFC is also consistent with the type of memory deficits seen in patients with frontal lobe deficits, such as increased susceptibility to interference (Gershberg and Shimamura, 1995) and high false alarm rates (Schacter et al, 1996), and the haemodynamic responses in this region have been suggested to be a correlate of the right frontal old/new ERP effect (see above; also Rugg et al, 2002).

Medial Temporal Lobe

In contrast to the neuropsychological evidence for the crucial role of medial temporal lobe structures in episodic retrieval, relatively few efMRI studies have found evidence for engagement of this region during simple recognition tasks (though see Cabeza et al, 2001; Donaldson et al, 2001). However, other studies using more complex retrieval tasks, and separating effects of recollection and familiarity have been more successful in revealing effects in MTL.

Using an R/K procedure, Eldridge and colleagues (2000) reported significantly greater hippocampal activity in trials associated with recollection vs. familiarity, consistent with the view that activity in this region increases with amount of information retrieved (Schacter et al, 1996; Rugg et al, 1997a; Stark and Squire, 2000). Buckner and Wheeler (2004) also used an R/K paradigm to investigate correlates of recollection and familiarity. One of the areas showing significantly greater activation for trials attracting R than K judgements was right parahippocampal gyrus, adding support for a role of the hippocampal formation in recollection. It should be noted that another study using R/K failed to elicit differential activity in MTL for R and K trials (Henson et al, 1999), although strong conclusions cannot be drawn on the basis of such a null result.

A number of recent studies using source memory paradigms have also reported MTL activity associated with accurate vs. inaccurate source memory. Cansino et al (2002) examined recognition and source memory for pictures which had been presented at different spatial locations during encoding. They reported effects in right hippocampal formation reflecting accurate vs. inaccurate source memory. Similarly, a study by Kahn and colleagues (2004) tested item and source memory for words encoded under one of two encoding conditions (either reading the word or creating a mental image of the thing represented by the word). Recognised words attracting correct vs. incorrect source judgements were associated with activity in the left parahippocampal region. Finally, one study used differing retrieval tasks, where subjects had to either discriminate words according to the encoding task (reliant upon recollection) or their relative recency. Left hippocampus responded to correctly classified items on the task discrimination, but not the recency discrimination (Dobbins et al, 2003).

While source and R/K tasks have, in some cases, found evidence for MTL involvement in recollection, it may be the case that hippocampus is particularly crucial for retrieval of associations when these are across different modalities. Hippocampal activity has been reported in studies examining retrieval of picture-word (Gabrieli et al, 1997; Stark and Squire, 2000), picture-sound (Nyberg et al, 2000; Wheeler et al, 2000; Vaidya et al, 2002) and picture-odour associations (Gottfried et al, 2004).

One factor which may reduce the likelihood of finding old/new differences in simple recognition tasks is that the hippocampus is known to be involved with memory encoding (e.g. Stern et al, 1996; Gabrieli et al, 1997; Otten et al, 2001) and has been shown to encode new items during a recognition task (Stark and Okado, 2003).

Therefore overlapping regions may be performing functionally distinct tasks during an old/new recognition task but old/new contrasts do not reveal any effects as retrieval and encoding effects conceal one another.

While the focus of this section is on the correlates of episodic retrieval, reflected by recollection in recognition memory tasks, it is also worth noting a proposed correlate of familiarity processing in MTL. Studies of recognition in rodents and non-human primates have suggested that perirhinal cortex in the anterior MTL is responsive to the relative novelty or recency of cues, and is a candidate region for supporting familiarity processing (see Aggleton and Brown, 2001). As recollection and familiarity are considered independent processes, an unknown proportion of trials accompanied by recollection will also be associated with familiarity processing, making it more difficult to isolate familiarity than recollection. Familiarity responses would be expected in comparisons of correctly classified old and new items, but should be invariant between recollected and familiar trials (see Rugg and Yonelinas, 2003). A number of studies have reported effects with such properties, and though they differ in laterality and extent, they appear to show common decreased responses to old vs. new items in anterior MTL (see meta-review by Henson et al, 2003). These novelty responses are consistent with the animal findings, and suggest that perirhinal cortex is indeed a candidate for supporting relative recency discrimination thought to underlie familiarity. However, while these effects may reflect familiarity processing, it is possible that they might reflect other, implicit effects such as priming.

Summary

This chapter has introduced the concept of multiple memory systems, and the evidence for a system subserving the retrieval of prior episodes. There is strong evidence for a number of dissociable memory systems, and in particular for a system for retrieving long term memories in a form that allows explicit description of the retrieved information, which can be dissociated from long term implicit memory such as how to ride a bike, or priming of responses, as well as to short term (working) memory. There is also some evidence that memory systems for retrieval of facts (semantic memory) and episodes (episodic memory) are functionally and anatomically distinct, though this dissociation is less clearly established.

This chapter has also covered the use of recognition paradigms, which were employed in the work described in this thesis, and how the findings from such studies relate to episodic retrieval. Dual process models of recognition memory distinguish between recognition based upon acontextual familiarity and recollection of the encoding episode. There is considerable evidence that there are two phenomenologically distinct recognition experiences which may be associated with functionally distinct cognitive processes. Neuropsychological studies have implicated the hippocampus, and to some extent surrounding MTL structures, in recollection whilst perirhinal cortex may have a role in supporting familiarity. Functional imaging studies have identified both electrophysiological and haemodynamic correlates of retrieval processing. efMRI has identified areas of left lateral parietal cortex which appear to selectively correlate with episodic retrieval, with a left parietal positivity in ERPs to old vs. new items proposed as the electrophysiological correlate of this same process. Further findings from functional imaging studies have highlighted correlations of activity in prefrontal cortex reflecting processing contingent on successful retrieval of

information from memory (anterior PFC) and monitoring of retrieval attempts and guidance of behaviour (right DLPFC). fMRI evidence for dissociable roles of hippocampal and perirhinal MTL regions in supporting recollection and familiarity has also been discussed. These correlates of episodic recollection will be discussed again in reference to the findings from the studies reported in this thesis.

Chapter 2: Memory and Emotion

Introduction

This chapter discusses findings relating to interactions between memory and emotion. As will be discussed, memory for emotional items and events is likely to have survival value and consequently be crucial to our biological viability. The first area covered is the concept of emotion, and the various ways it can be defined and categorised. Evidence for the neural structures involved in emotional processing from both neuropsychological/ animal lesion studies and functional imaging work is then presented. The chapter then turns to findings from the most well studied example of emotional memory, the phenomenon of conditioning, before moving to experiments relating to episodic memory for emotional items and events, particularly focussing on retrieval which is the prime subject matter of this thesis. The discussion will cover emotional modulations of performance on episodic memory tasks, before addressing the cognitive processes and neuroanatomy underpinning emotional episodic memory. Finally, some of the outstanding issues in this field will be raised and the approach taken to resolving such issues in the present research discussed.

Concepts and Definitions of Emotion

Emotion has been one of the most difficult of cognitive domains to define, measure and provide testable hypotheses. This is reflected in the dearth of neuroscientific studies of emotion from the start of the 'cognitive revolution' in the 1950s until the late 1980s, when a number of researchers attempted to operationalise emotion within an objective framework. At a general level, it is uncontroversial to consider the role of the emotional system as ascribing value to environmental events, evaluating

whether such events influence an organism's state in an advantageous or disadvantageous manner. The range of emotions which can be expressed by an organism tend to reflect the complexity of its environment, such that social and cultural as well as physical contexts are crucial to emotional processing in humans (see Dolan, 2002). An ability to ascribe value, evident across phylogeny, represents a prime means of conferring evolutionary advantage. A prime medium by which such advantage is conferred is through the influence of emotion on memory. By way of example, the enhanced consolidation of a prior adverse occurrence can bias future behaviour in order to minimise the likelihood of future negative occurrences.

Despite the general consensus as to the role of emotion, defining different aspects of emotional processing, or providing an objective metric for its study has proved difficult. One crucial issue is the diversity of human emotional experience – Bower (1992) notes over 600 words in the English language referring to different affective experiences, which he suggests is too many for each of these experiences to be considered discrete. Two basic approaches have been employed to address this issue. One method is to attempt to define a small set of 'basic' or 'prototypical' emotions, of which all others can be considered to be subcategories or special cases of, whilst the second method has been to set a framework where emotions are described in terms of one or more different elements or aspects.

The definition of basic emotions, and the subsequent investigation of the behavioural, physiological and neural responses associated with experience of or exposure to each of these emotions, has certainly contributed to our understanding of emotional processing. Unfortunately, however, there is little consensus across the literature as to what constitutes a basic emotion (see Shaver et al, 1987 vs. Ekman, 1992 vs. Panksepp, 1992). For example, Ekman and colleagues have concentrated on facial

expressions, which appear to have common meaning across age and culture and are argued to be 'basic' in that the key exemplars are relatively independent of context. This work has led Ekman to define six basic emotions which can be recognised panculturally from facial expressions (happiness, surprise, anger, fear, disgust and sadness) though, for example, positive emotions which share highly similar facial expressions, may be discriminated according to vocal features. A further issue, which applies to emotion research in general, is the distinction between experience of an emotion and processing of emotional stimuli depicting such reactions (Damasio, 1995). Whilst it seems probable that these processes partly overlap in terms of their cognitive and neural substrates, it may not be the case that they are identical. In addition to the lack of consensus as to the basic emotions, the approach suffers from ignoring commonalities amongst different emotions, which may be reflected in their processing. An example of a taxonomy incorporating the basic emotion concept is illustrated in figure 2.1.

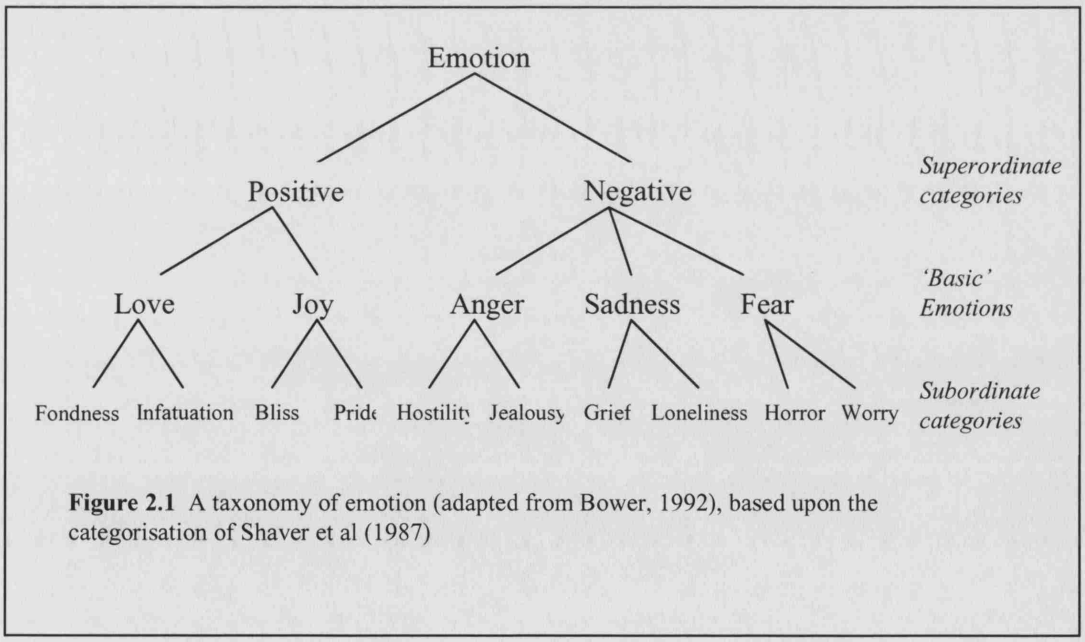

Figure 2.1 A taxonomy of emotion (adapted from Bower, 1992), based upon the categorisation of Shaver et al (1987)

An alternative approach is to view emotions in a framework consisting of different elements or dimensions which describe aspects of them, such as their value or the contingent behavioural response. These elements are shared across a range of diverse emotions (see e.g. Ortony and Turner, 1990; Lang et al, 1990; Davidson et al, 1990; Armony and LeDoux, 2000). One proposed element is valence, that is the biological or social 'value' of eliciting stimuli. The term valence has been employed in different ways within the literature – in its simplest form, stimuli may be considered negatively, positively or neutrally valenced. Alternatively, valence can be considered a continuous dimension, ranging from extremely negative, through moderately and mildly negative, neutral and so on to extremely positive. This allows a distinction between the direction of valence and the absolute valence i.e. the degree to which a positive or negative event differs from neutrality.

A distinction which overlaps considerably with positive vs. negative valence is whether stimuli elicit approach or avoidance behaviour. Approach behaviours maximise the effects of eliciting stimuli, whereas avoidance behaviours minimise their effects. As might be expected, most emotions classified as positive elicit approach behaviours, and negative elicit avoidance, but there are cases where the two approaches do not converge. A case in point is anger which is a negative emotion, yet elicits approach behaviour. The usefulness of such approaches is evident in studies showing that patterns of brain activity may depend on whether stimuli were positive or negative (e.g. Canli et al, 1998) or whether they elicited approach or avoidance behaviour (e.g. Fox and Davidson, 1988).

Another dimension considers how occurrences affect the current motivational state of the organism. In this framework emotions are considered by-products of an organism selecting goal directed actions to deal with its current needs (Bower, 1992).

Occurrences appraised as aiding the satisfaction of underlying motivational states produce positive emotions, whilst negative emotions result from obstacles to satisfaction of motivational goals, or from the absence of expected positive goals.

Finally, a commonly employed dimension is that of 'arousal', to index the intensity of the emotional response elicited, from calm at one extreme to aroused at the other. Arousal is the element which correlates most strongly with peripheral autonomic measures such as the galvanic skin response (GSR) and heart rate (see Bauer, 1998 for review). Different elements may be combined in order to describe a space within which emotions reside, for example Lang and colleagues describe emotional stimuli within a 2-dimensional framework of valence and arousal (e.g. Bradley et al, 1992; Bradley and Lang, 1994; Cuthbert et al, 1996).

Although the approaches outlined above are rarely combined, aspects of them are reconcilable. A number of distinct classes of emotion can be recognised, which may be considered as lying within distinct regions of an emotion space defined by a number of different characteristics. Emotions consist of the neural, behavioural and hormonal responses to ongoing events and may be subserved both by integrated neurobiological sub-systems (subserving processes such as arousal or approach and avoidance responses) and processes specific to particular emotions.

The Neuroanatomy of Emotion

There is evidence from neuropsychological, animal lesion and functional imaging studies for the involvement of circumscribed neural structures in the processing of emotion. Some of these findings will be discussed here and an overview presented of

the circuits most commonly considered part of the emotional system (for reviews see Phan et al, 2002; Patterson and Schmidt, 2003).

Evidence for a role of temporal lobe structures in emotional processing first emerged from the findings of Kluver and Bucy (1939), who described a syndrome (Kluver-Bucy syndrome) characterised by passiveness, hyperorality and hypersexuality in monkeys following temporal lobe lesions. Despite later findings that some of the symptoms reflected effects not directly related to emotional processing, it was found that some elements could be reliably reproduced by lesions restricted to the amygdala (Weiskrantz, 1956). The amygdala is a small ovoid subcortical structure in the anterior portion of the medial temporal lobe, consisting of a number of functionally distinct subnuclei. While there are a large number of these subnuclei, they are often segregated into 3 principal subregions – the lateral amygdala (LA), basolateral amygdala (BLA) and central amygdala (CeA). These regions appear to have different roles which we will discuss shortly, but in general the amygdala can be viewed as being crucial for the association of the affective properties of stimuli with their sensory representations (Weiskrantz, 1956).

Bilateral lesions restricted to the amygdala are extremely rare, though comparisons of deficits in patients with medial temporal lobe lesions which either do or do not include the amygdala can be used to infer its contribution. Some patients however do exhibit pathology restricted, at least in early stages, to the bilateral amygdala. The key example is the Urbach-Wiethe syndrome, a rare lipoprotein disorder which is associated, in around 50% of cases, with symmetrical calcification of the amygdala (see Siebert et al, 2003). Such damage is associated with impaired recognition of emotional facial expressions (e.g. Adolphs et al, 1994; 2002; Adolphs and Tranel, 2004) and impaired memory for emotional items (Siebert et al, 2003; Strange et al,

2003). It has been suggested that the amygdala damage particularly impairs memory for the emotional gist of stimuli, without affecting the ability to remember visual details (Adolphs et al, 2001).

However, amygdala damage does not disrupt all aspects of emotional processing - the particular emotional facial expressions showing impaired recognition are inconsistent across studies (e.g. Siebert et al, 2003 vs. Adolphs and Tranel, 2004), while valence ratings of emotional pictures (Siebert et al, 2003) and description of subjective emotional states (Anderson and Phelps, 2002) do not differ significantly from those of normals. This may reflect, at least in part, development of alternative cognitive strategies to compensate for impaired affective processing.

Unilateral lesions of the amygdala are sometimes associated with deficits in emotional processing, but these are more subtle and less consistent than in patients with bilateral damage (see e.g. Adolphs and Tranel, 2004; Adolphs et al, 2001). Studies of patients with unilateral damage have provided some evidence for different roles of left and right amygdala in emotional processing. For example, Funayama and colleagues (2001) have suggested that left amygdala is specialised for processing verbally-mediated emotional information, and right amygdala for non-verbal emotional information, analogous to the roles proposed for left and right hippocampus in verbal and non-verbal memory respectively (e.g. O'Keefe and Nadel, 1978). On the other hand, Gläscher and Adolphs (2003) have proposed that right amygdala is automatically engaged by emotionally arousing stimuli, even if they are only processed subliminally, whilst left amygdala is important for decoding the emotional significance of such stimuli. There is no clear consensus on such lateralisation of amygdala function, though we will revisit this issue later in light of functional imaging findings.

Functional imaging studies have revealed activation of the amygdala is response to a variety of emotional stimuli, including emotional words (e.g. Hamann and Mao, 2002), photographs (e.g. Garavan et al, 2001), and fearful faces (e.g. Breiter et al, 1996; Morris et al, 1996). Amygdala activity has also been shown to correlate with subjective ratings of valence during evaluation of emotional stimuli (e.g. Phan et al, 2004). These findings suggest a role for the amygdala in supporting emotional processing this structure will be revisited when discussing the emotional memory findings.

Besides the amygdala, another area which has attracted much interest in emotion research is the prefrontal cortex. A possible role for this region in emotional processing was suggested in the 19th Century by the case of Phineas Gage (described in Damasio et al, 1994), who exhibited marked social and behavioural changes after severe damage to his frontal cortex in an accident. Extensive studies of patients with frontal damage have confirmed that such individuals often show altered social and emotional behaviour, such as impulsiveness, jocularity, irritability, inappropriate sexual behaviour and misinterpretation of other people's moods (e.g. Damasio et al, 1990; Rolls et al, 1994; Hornak et al, 1996). There is also evidence that lesions to left and right frontal cortex may have dissociable effects on behaviour (see Gemar et al, 1996). Two common syndromes arising from frontal lobe lesions are 'pseudodepression' (reduced emotional expressiveness, apathy, loss of initiative and sex drive) and 'pseudopsychopathy' (impulsiveness, irritability, mania, socially and sexually inappropriate behaviour, jocularity), with a prevalence of the former following left frontal lobe lesions (e.g. Sackeim et al, 1982; Robinson and Chait, 1985; see also Davidson and Irwin, 1999; Davidson et al, 1999), and a greater incidence of pseudopsychopathy after right frontal lesions (e.g. Cohen and Niska,

1980; Sackeim et al, 1982; Gillig et al, 1988; see also Davidson and Irwin, 1999; Davidson et al, 1999). Further support for possible lateralisation of emotional processing in prefrontal cortex comes from neuroimaging studies of depression, showing decreased blood flow in left prefrontal cortex associated with negative mood, and that recovery from depression is associated with normalisation of blood flow in this area (Bench et al, 1992; 1993; 1995).

Orbital and ventromedial areas of prefrontal cortex are particularly strongly associated with emotional processing (see Bechara et al, 2003). Damage to these regions is associated with deficits in identification and production of emotional expressions (e.g. Hornak et al, 1996; Angrilli et al, 1999), and abnormal autonomic responses to stimuli which have acquired, but not intrinsic, emotional significance (e.g. Damasio et al, 1990). Orbitofrontal cortex has also been associated with regulation of mood states in both neuropsychological (e.g. Drevets et al, 1992) and neuroimaging studies (e.g. Pardo et al, 1993; Baker et al, 1997). There is also strong evidence for the involvement of orbitofrontal cortex in processing of reward (Rolls et al, 1980; Schultz et al, 1998; O'Doherty et al, 2002) and decision making in risk assessment/gambling tasks (Rogers et al, 1999; O'Doherty et al, 2001; Cavedini et al, 2002). These functions may be particularly relevant to the role of orbitofrontal cortex in emotional memory processing, which will be discussed shortly. The amygdala and orbitofrontal cortex have received the most attention and are probably the most important structures for emotional processing, and for emotional memory, but a number of other regions are important in emotional processing as will be discussed now.

A number of areas concerned with autonomic and endocrine regulation have reciprocal connections with the amygdala and are important in expressing the physiological responses to emotional events. These physiological components of the

emotional response are considered to be integral to the experience of emotion (see James, 1890; Lang et al, 1993; Dolan, 2002). Evidence for the importance of these responses comes from patients with peripheral autonomic failure (PAF) who have subtle blunting of emotional experience, and show reduced neural responses to emotional stimuli (Critchley et al, 2001; 2002). Important regions in generating and monitoring these responses include the hypothalamus and the brainstem.

The insula is another region which shows activity correlated with autonomic measures (Critchley et al, 2000a;b), that has also been associated with processing pain (Oshiro et al, 1998; Davis et al, 1998; see Peyron et al, 2000 for review) and internal generation of emotion (Reiman et al, 1997). It may be that insula is important in monitoring internal states, and has been proposed as important in the subjective experience of emotion, or 'feelings' (Damasio, 1995; 1999). This region has also been proposed to play a specific role in the processing of disgust (Phillips et al, 1997; Calder et al, 2000).

The anterior cingulate cortex (ACC), particularly the rostral part, is also sensitive to emotion (e.g. Whalen et al, 1998), and is typically associated with emotional tasks which have high cognitive demand (see Phan et al, 2002). This region is known to modulate attention and executive functions, and has been proposed to act as a regulatory interface between emotional and cognitive processing. For example, cognitive evaluation of emotional stimuli, which tends to decrease their emotional impact, is associated with correlated increases in ACC activity and decreases in amygdala activity (Hariri et al, 2003).

The structures of the basal ganglia (striatum, globus pallidus, substantia nigra and subthalamic nucleus) have outputs to the motor system and are particularly associated with processing reward (e.g. Breiter et al, 1997; Phillips et al, 1998; Rolls, 2000; Lane

et al, 1999; O'Doherty et al, 2004) and disgust (Phillips et al, 1998; Sprengelmyer et al, 1998). These areas may be important in coordinating appropriate withdrawal or approach behaviours in response to emotional stimuli. Finally, some of the emotional modulations induced by the amygdala in particular may not be mediated through direct connections but via release of neuromodulators from basal forebrain (acetylcholine), locus ceruleus (noradrenaline), midbrain (dopamine) and raphe nuclei (5-hydroxy-tryptamine (5-HT)). Therefore these regions may also be important in mediating components of the integrated response that constitutes emotion.

Having reviewed the main brain regions involved in emotional processing, we will now focus on emotional memory, first addressing findings from conditioning studies.

Conditioned Emotional Responses

The phenomenon of conditioning was first described by Pavlov (1927), who described how the temporal pairing of neutral stimuli with positive or negative emotional experiences led to these stimuli acquiring emotional significance and eliciting emotional responses themselves. However, it was not until the late 1970s that Pavlovian conditioning paradigms became widely used to study emotion. The most widely studied form of this is fear conditioning, in which an emotionally neutral conditioned stimulus (CS) is presented in conjunction with an aversive unconditioned stimulus, typically a weak electric shock or white noise. After one or more pairings, the CS acquires the ability to elicit a range of responses typical of those occurring in the presence of danger, including behavioural (e.g. freezing or escape responses), autonomic (e.g. GSR, blood pressure and heart rate) and neuroendocrine responses (e.g. release of corticosteroids and adrenaline). These responses are innate, species-

typical responses which are expressed automatically in the presence of appropriate stimuli. Therefore fear conditioning allows the deployment of evolutionarily tuned responses to danger in response to newly acquired threats (which the CS has become, as a predictor of the UCS). Conditioning may occur whether presentation of the CS and UCS overlap temporally ('delay conditioning') or whether CS presentation has terminated prior to a UCS onset ('trace conditioning'). Neural activity associated with conditioning may be modulated by whether there is conscious awareness of the contingency between CS and UCS (e.g. Morris et al, 1998), but conditioning can occur without such awareness (e.g. Morris et al, 1998; Knight et al, 2003). In addition to the CS being able to elicit conditioned emotional responses, these may also be observed when an animal returns to an environment where it experienced a UCS, a phenomenon known as contextual conditioning (see Kim and Faneslow, 1992; Phillips and LeDoux, 1992; Maren et al, 1997). We will consider the importance of different brain structures for these forms of conditioning in rodents, which have been most widely studied, and then discuss how these relate to those in humans.

A large number of studies have shown that damage to the amygdala impairs the acquisition and expression of conditioned fear (see LeDoux, 2000; Maren, 2001). As discussed earlier, the amygdala consists of a number of subnuclei, with different anatomical connections and functions (summarised in fig 2.2; for review see McDonald, 1997). Most of the sensory inputs to the amygdala terminate in LA (e.g. Turner et al, 1980; LeDoux et al, 1990; Amaral et al, 1992), and damage to this subregion alone has been shown to interfere with conditioning (LeDoux et al, 1990; Campeau and Davis, 1995). Damage to the CeA also interferes with the expression of conditioned fear responses (Gentile et al, 1986; Hitchcock and Davis, 1986; Van de Kar et al, 1991). This area serves as the interface with motor, autonomic and

endocrine output systems. Lesions to structures downstream of CeA selectively interfere with the expression of different aspects of the conditioned response – lateral hypothalamus lesions prevent the normal changes in blood pressure, but do not affect freezing, whilst the opposite pattern is observed following damage to the periaqueductal gray (PAG) (LeDoux et al, 1988), whilst the stria terminalus affects neither of these measures, but is crucial for the release of stress hormones from the pituitary-adrenal axis (Van de Kar et al, 1991).

In contrast, lesions of BLA may not interfere with simple auditory fear conditioning (Majidishad et al, 1996), but interfere with contextual fear conditioning (Majidishad et al, 1996; Maren and Faneslow, 1995). The BLA has reciprocal connections with cortical emotion processing structures, such as orbitofrontal cortex (Carmichael and Price, 1995), and with the hippocampus (Canteras and Swanson, 1992). Lesions of either the amygdala or hippocampus prevent contextual conditioning, but the hippocampus is not necessary for simple fear conditioning (Kim and Faneslow, 1992; Phillips and LeDoux, 1992; Maren et al, 1997; Anagnostaras et al, 2001).

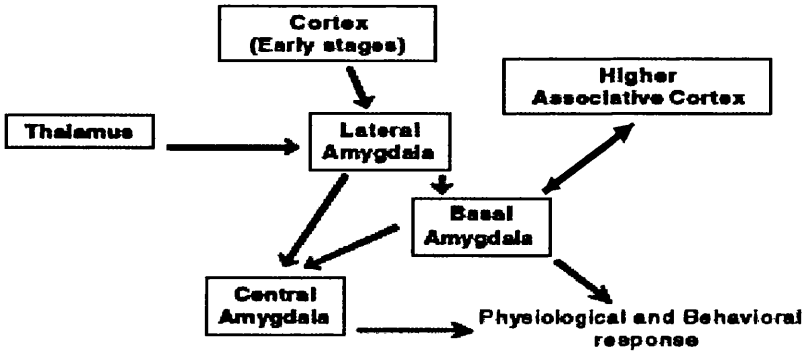

Fig 2.2 Simple model of amygdala connectivity. Adapted from Richter-Levin (2004)

Studies of plasticity in amygdala and amygdala-hippocampal pathways support the view that conditioning leads to long term changes in neural pathways. In vivo recording of field potentials in LA have shown that LTP induction and fear conditioning result in similar changes in processing of a CS (Clugnet and LeDoux, 1990; Rogan and LeDoux, 1995; Rogan et al, 1997). LTP has also been identified in hippocampal amygdala pathways, believed to be involved in contextual conditioning (Maren and Faneslow, 1995). However, whether amygdala plasticity is crucial for fear conditioning, or the role of the amygdala is principally confined to modulating memory systems elsewhere in the brain remains a source of debate (e.g. Cahill and McGaugh, 1998; Faneslow and LeDoux, 1999).

A considerable number of studies provide evidence that the amygdala plays a critical role in fear conditioning in humans (LaBar et al, 1995; 1998; Phelps et al, 1998; Büchel et al, 1999). Amygdala activity has been observed during the establishment and extinction of CS/UCS contingencies (e.g. LaBar et al, 1998) and responses to fear conditioned stimuli (e.g. Büchel et al, 1999). As discussed above, the amygdala has connections with sensory, autonomic and memory systems, and is proposed to subserve three different functions in fear conditioning: firstly evaluating the affective significance of stimuli, secondly controlling physiological responses and thirdly sensitisation of neural processing to stimuli with acquired emotional value i.e. memory (see McGaugh et al, 1996; Cahill et al, 1999; see also Davis, 1997; Faneslow and LeDoux, 1999; LeDoux, 2000 for variations on this view). Patients with bilateral damage to the amygdala fail to show normal changes in skin conductance response to conditioned stimuli (Phelps et al, 1998), despite normal performance on episodic memory tasks (see LaBar et al, 1995) implying that the deficit cannot be due to simple failure to remember the conditioned stimulus. This pattern is reversed in patients with

hippocampal damage, who show normal changes in GSR after conditioning, despite impaired episodic memory (Bechara et al, 1995). Therefore fear conditioning at least, is not dependent on explicit retrieval of CS/UCS contingencies, and there is also evidence that conditioning can occur in the absence of awareness of these contingencies during the conditioning procedure, as shown by studies using 'masked' or subthreshold stimuli (Morris et al, 1998; 2001; Critchley et al, 2002a; Knight et al, 2003).

While conditioning studies have primarily used aversive, particularly fearful, stimuli a considerable amount of work has also been carried out examining appetitive conditioning, using both classical/Pavlovian approaches and operant conditioning paradigms in which the outcome, such as receipt of a reward, is dependent on an action, such as pressing a lever, in response to the conditioned stimulus. The dopaminergic system has been a particular focus of attention because of the importance of dopamine in addiction and drug-seeking behaviour (e.g. Bozarth and Wise, 1983; Stewart, 1983; Ito et al, 2002). A number of studies by Schultz and colleagues have confirmed the involvement of dopaminergic neurons in appetitive conditioning by recording activity from various neural populations in non-human primates. Dopaminergic neurons in the A10 nucleus of the substantia nigra show phasic responses to receipt of reward (UCS) during learning of CS/UCS associations, but fewer are responsive to the reward after training. They also respond to the CS during and after learning, suggesting that these neurons respond to stimuli with behavioural significance rather than reflecting actual receipt of reward, or anticipatory or preparatory processes (Schultz et al, 1993). This view is reinforced by the findings of Hunt and McGregor (1998) that when rewarding events are predictable they do not induce significant increases Fos-immunoreactivity in rat dopaminergic neurons.

Dopaminergic neurons have also been shown to reflect reward probability and uncertainty (Fiorillo et al, 2003) and to respond to the omission of expected rewards (Tobler et al, 2003).

These dopaminergic neurons project to a number of regions including the basal ganglia, amygdala, prefrontal cortex and thalamus, which have been proposed as a 'motive circuit' mediating perception of reward and initiation of appropriate behavioural responses (see Kalivas and Nakamura, 1999). Neurons in both the basolateral amygdala (Pratt and Mizumori, 1998) and medial prefrontal cortex (Pratt and Mizumori, 2001) of the rat are sensitive to differential rewards in spatial memory tasks, while lesions of the central amygdala disrupt expression of orienting responses to conditioned stimuli.

There are few studies of appetitive reinforcement and conditioning in humans, but these also suggest roles for the dopaminergic system, amygdala, orbitofrontal cortex and striatum. Cues signalling delivery of pleasant rewards can elicit haemodynamic responses in dopaminergic regions of the midbrain, dorsal amygdala, striatum and OFC, but of these areas only the OFC was shown to be responsive to reward receipt per se (O'Doherty et al, 2002). Similarly, Gottfried and colleagues (2002) employing an olfactory classical conditioning task reported engagement of anterior and medial OFC, striatum and amygdala. Further work has suggested that OFC and amygdala activity specifically reflects the reward value predicted by a conditioned stimulus (Gottfried et al, 2003), while ventral striatum has been proposed to detect discrepancies between predicted and actual rewards with dorsal striatum specifically involved in processing goal-directed actions in response to conditioned stimuli (O'Doherty et al, 2004).

It seems clear from the conditioning findings that a number of structures, particularly the amygdala and regions of prefrontal cortex, are implicated in emotional memory processing. However, whilst conditioning is a useful form of emotional memory to study it is normally classified as a form of implicit memory and, except in the case of contextual conditioning, it is not dependent on explicit retrieval of emotional associations of conditioned stimuli (though responses may be modulated by awareness; see above). We will now discuss the findings from studies which have specifically addressed the retrieval of emotional episodes.

Emotional Episodic Memory

While most studies of emotional memory have used conditioning paradigms, the modulation of episodic memory by emotion has also been investigated. All of us have conscious memories of emotionally arousing events, positive and negative, which are particularly vivid and well remembered. A considerable number of studies have demonstrated that emotional memories are better remembered than their neutral counterparts (see Christianson, 1992 for review). For example, when subjects are presented with stories in slides, of differing emotional content, a greater amount of detail is recalled from the emotional slides (Heuer and Reisberg, 1990; Burke et al, 1992). Likewise, memory for emotional words (Phelps et al, 1997) and pictures (Hamann et al, 1997) is enhanced compared to neutral equivalents. In some cases the strength of emotional memories may be pathological, for example patients suffering from post-traumatic stress disorder (PTSD) may suffer from undesired and uncontrollable retrieval of highly aversive events (e.g. Burstein, 1985).

In general, emotion enhances free recall to a greater degree than recognition (e.g. Danion et al, 1995), and indeed recognition advantages for emotional items are only found inconsistently (e.g. Hamann et al, 1999 vs. Danion et al, 1995). In addition to emotion-related differences between emotional and neutral items, other factors may also contribute to these effects. For example, emotional words tend to be better remembered than their neutral counterparts even when they are not significantly more arousing (as indexed by GSR), because they tend to be more semantically cohesive. When cohesion is controlled for, the retrieval advantage for low-arousal emotional words can be eliminated (Phelps and LaBar, 1997).

It is worth noting that, in addition to its enhancing effects on memory, emotion also interferes with memory processing. Some individuals experiencing extremely stressful events may develop post-traumatic amnesia (PTA), being unable to remember or describe these occurrences. It has been shown in animal models (e.g. Conrad et al, 1997) that administration of the stress hormone corticosterone (the rodent analogue of cortisol), or a glucocorticoid agonist, prior to learning may impair later memory for learnt material. Likewise, the work of Strange and colleagues (2003) has shown that where lists of neutral, semantically related words have emotional and semantic 'oddball' words interspersed during encoding that memory for words presented immediately prior to emotional oddballs is selectively impaired. This 'E-1'

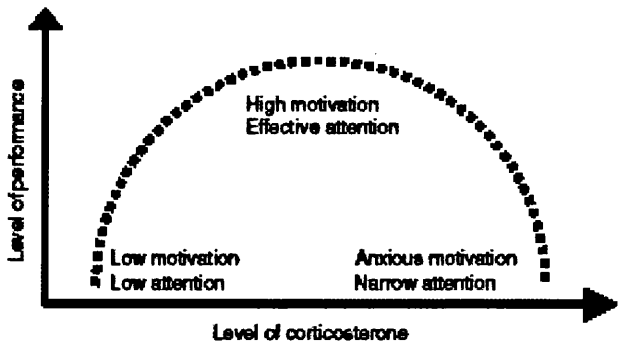

Figure 2.3 Possible model of emotion/stress effects on task performance, such as during encoding of emotional stimuli. At moderate levels of arousal, attention is well focussed and enhances task performance. At high levels, attention is excessively focussed, impairing performance. After Richter-Levin (2004)

effect, can be abolished by administration of a β-adrenergic antagonist during encoding (Strange et al, 2003), as can enhanced memory for emotional items (Cahill et al, 1994), suggesting similar mechanisms, at a neurochemical level at least, for emotion related enhancements and decrements. It seems likely that the influence of emotional arousal on memory demonstrates an 'inverted U' pattern (see fig 2.3), such that optimal encoding of events occurs at moderate levels of arousal, with low levels being associated with low motivation and limited deployment of attentional resources, while high arousal may lead to inefficient processing due to excessive focussing of attention on arousing stimuli (see also Richter-Levin, 2004).

Although many of the above findings might be explained in terms of engaging attentional processes, there are also emotion and valence-specific influences on memory processing. For example, emotional items show enhanced memory compared to high interest neutral items which rate as significantly less emotional, but not less interesting or attention-grabbing (Hamann et al, 1999). Valence specific effects are revealed by findings of improved memory for material which is matched in valence with the mood of a subject during retrieval (Bower, 1981; Dietrich et al, 2000), while affective disorders such as depression are associated with mood congruent memory bias (see Blaney, 1986).

There is considerable support for modulation of episodic memory by emotion, and the neural basis of these effects is now discussed. In addition to identifying the structures and processes involved, there are issues of interaction with systems underlying non-emotional memory processing, and the time at which emotion may have its effects. One question is whether some types of emotional memory may be stored by systems distinct from those required for neutral memories (i.e. the sites of plasticity differ), or whether both are stored by a common memory system, which can be modulated by

structures that mediate emotional processing (e.g. Cahill et al, 1999 vs. Faneslow and LeDoux, 1999; see also Richter-Levin, 2004). Another consideration is the stage of processing at which emotion and memory interact – effects that may occur during encoding, consolidation and retrieval of emotional memories, or be restricted to one or more stage.

As with the conditioning studies discussed above, the amygdala has received much attention as a critical structure in emotional episodic memory. If normal subjects are shown a series of slides depicting a story, they show enhanced memory for slides with emotional content. Patients with damage to bilateral amygdala, or with left lateralised damage, fail to show this normal facilitation (see Adolphs et al, 2000). Together with findings from patients with MTL amnesia (Hamann et al, 1997a) and Alzheimer's disease (AD) (Kazui et al, 2000), who show impaired performance on memory tasks generally, but still show a facilitation of performance for the emotionally valenced slides, this suggests dissociable roles for hippocampus and amygdala similar to those described for classical conditioning and spatial memory in rodents, implying amygdala as a crucial site of plasticity. However, another study found that patients with AD did not show the normal facilitation of performance for emotional material (Hamann et al, 2000). It may be that the patients' amygdale, which are damaged during the progression of AD albeit generally later than entorhinal and hippocampal damage begins, had suffered on average greater damage in the study by Hamann and colleagues (2000) than in the study of Kazui and colleagues (2000). It is likely that if parts of both the episodic memory system and amygdala are still able to function effectively then emotional enhancement of memory is still preserved. While implicit emotional memories, for fear-related stimuli in particular (see LeDoux, 2000; Maren, 2001 for reviews), may be accounted for by amygdala plasticity alone, formation of

explicit memories of emotional events likely depends on plastic changes both within amygdala and hippocampus, and interactions between these structures (Dolcos et al, 2004; Richardson et al, 2004; see also Richter-Levin, 2004; Phelps 2004).

However, despite the above considerations, the amygdala does not appear to be necessary for emotional enhancement of all forms of episodic memory. Phelps and colleagues (1997; 1998) have shown that patients with unilateral temporal lobe damage, or with bilateral amygdala damage show recognition advantages for emotional words and neutral words encoded in emotional sentences which are equivalent to those seen in control subjects. Such effects may be due to emotional stimuli being more easily organised within a schema than neutral equivalents, and hence showing improved levels of recall. However, it is noteworthy that in these experiments, subjects did not rate emotional stimuli as being highly arousing. In contrast, when highly arousing 'taboo' words or emotional slides were used to test memory, bilateral amygdala damage significantly impaired memory for emotional stimuli compared to controls (Phelps et al, 1998). This suggests that arousal is a key component in amygdala-related enhancement of emotional memory, but that other areas may support alternative processes enhancing memory for emotional items and events. Such a proposal is supported by the findings of Kensinger and Corkin (2004) who compared neural activity underlying emotional enhancement of memory for arousing and non-arousing emotionally valenced material. Their findings suggest that interactions between amygdala and hippocampus underlie the effects of emotional arousal on memory, while memory enhancement for non-arousing emotional material appears to depend on hippocampal-prefrontal interactions.

Evidence is now discussed for a role of the amygdala, and other emotion processing regions, during encoding, consolidation and retrieval of emotional episodic memories.

Encoding

The encoding of emotional memory has probably received the greatest attention in the literature. As discussed in chapter 1, one crucial factor for encoding stimuli effectively is the degree of attention which they are afforded. Emotion influences attention both in capturing attention, and prioritising the processing of emotional stimuli under conditions of limited attention (e.g. Fox et al, 2001; Ohman et al, 2001), both factors which should facilitate encoding relative to neutral stimuli. One paradigm which has been used to investigate influences on attention is the 'attentional blink' paradigm where subjects attempt to attend to specific targets in a rapidly presented stream of stimuli, where there is an enhanced probability of missing the second target if it is presented soon after the first. This has been interpreted as reflecting a limit of attentional resources within a particular time frame. If the second stimulus is emotional then attentional impairments are attenuated in normal subjects, but this is not seen in patients with damage to the amygdala (Anderson and Phelps, 2001).

The amygdala responds rapidly to emotional stimuli, and can do so without conscious awareness of eliciting stimuli (e.g. Whalen et al, 1998; Morris et al, 1998a) and when attention is focussed elsewhere (e.g. Vulleumier and Schwartz, 2001; Vulleumier et al, 2001; Anderson et al, 2003). These findings suggest that one crucial function of the amygdala is to enable emotional stimuli to have privileged access to cognitive resources, which will enhance their encoding. Additionally, amygdala activation may have effects in lowering the threshold for effective encoding of emotional stimuli. As discussed in chapter 1, plastic changes underlying memory formation result from Ca^{2+}-dependent molecular cascades in the post-synaptic cell, through either NMDA or

voltage gated ion channels, both of which require strong post-synaptic depolarisation to open. Cells in the dentate gyrus (DG) and cornu ammonis (CA) of the hippocampus have post-synaptic receptors for a number of neuromodulators, and release of these transmitters either directly or via amygdala influences on neuromodulatory nuclei, may provide a mechanistic basis for improving the chance that emotional events are effectively encoded. The adrenergic system is strongly implicated in mediating such interactions, with administration of a β-adrenergic antagonist during encoding appearing to eliminate the modulatory effects of emotion on memory, both in terms of its enhancing (Cahill et al, 1994) and amnestic effects (Strange et al, 2003). Glucocorticoid hormones may also have an important role in modulating encoding, as suggested by the findings of Buchanan and Lovallo (2001), who reported that administration of cortisol prior to training enhanced learning for emotional, but not neutral items. However, the time course of endogenous cortisol release implies that this may reflect an interaction of an aroused state with item-specific emotional processing, rather a direct effect on encoding of specific emotional items.

A number of functional imaging studies have shown that amygdala activity during encoding predicts how well emotional, but not neutral, stimuli will be subsequently remembered (e.g. Cahill et al, 1996; Hamann et al, 1999; Canli et al, 2000). Such activity also predicts memory for neutral stimuli encoded in emotional contexts (Erk et al, 2003).

Further to the findings above, it has been shown that during encoding of emotional events, the amygdala interacts with areas associated with the encoding of episodic memory. Kirkpatrick and Cahill (2003), using structural equation modelling, have shown functional connectivity between amygdala, parahippocampal cortex and

ventrolateral prefrontal regions during encoding of emotional but not neutral memories, suggesting that interactions between these regions are important for formation of emotional memories. The concept of interactions between amygdala and the episodic memory system is further strengthened by findings that activity in hippocampus during encoding of emotional, but not neutral, stimuli is modified by damage to the amygdala, and vice versa, showing correlations between activity in one structure and degree of damage to the other (Richardson et al, 2004).

Overall, there is compelling evidence that encoding of emotional events is associated both with enhanced allocation of attentional resources and modulation of episodic memory processing. The net effect is enhanced encoding, for which the amygdala appears to be the most critical structure.

Consolidation

While emotional memories tend to be more prominent than their neutral counterparts for recent events, those memories which persist over a long period of time are particularly likely to be those with emotional significance. A number of studies in animals and humans suggest that emotion enhances consolidation of memories (see Cahill and McGaugh, 1998 for review), supported by some direct behavioural evidence that the mnemonic advantage for emotional items and events tends to increase over time (Hamann et al, 1999). These consolidation effects are strongly tied to the encoding findings discussed above – the molecular cascades initiated by modulatory influences on hippocampal cells initially lead to relatively short term increases in synaptic strength, but over time are associated with more enduring changes, such as dendritic growth. It has been proposed that hippocampal synapses

activated during emotionally charged experiences may be 'tagged' by amygdala modulation of activity, increasing the strength of long term synaptic change (Richter-Levin and Akirav, 2000; 2003). This consolidation however is influenced not only by emotional responses at the time of learning, but also subsequent to it. Cahill and colleagues have identified that administration of adrenaline (Cahill and Alkire, 2003) or an aversive stimulus (Cahill et al, 2003) after encoding leads to further enhancement of memory for emotional but not neutral stimuli. However, it should be noted that administration of drugs blocking β-adrenergic receptors, which impair emotional encoding, has not been found to impair emotional memory when given during the consolidation period (van Stegeren et al, 2002). Nonetheless, there is significant evidence that the emotional system continues to modulate episodic memory processes after initial learning, allowing emotional memories to be particularly enduring over time.

Retrieval

Retrieval of emotional memories is the least widely studied aspect of affective-mnemonic interactions. It is difficult, if not impossible, to draw definitive conclusions about separate influences on encoding and retrieval by emotion on the basis of neuropsychological studies. Nevertheless, some evidence is emerging that whilst patients with amygdala damage are able to describe autobiographical memories with emotional content formed prior to such damage, they tend to show bias in the type of events described, and their descriptions are more factual and less emotionally laden than is typical in control subjects (T. Buchanan, personal communication).

A number of functional imaging studies have reported activity associated with retrieval of emotional information. Reiman et al (1997) used PET to examine activity related to induction of emotion by comparing blood flow changes associated with viewing emotional and neutral films, and remembering emotional and neutral episodes. Emotional (versus neutral) films and memories were associated with increased activity in medial PFC and thalamus, whilst an interaction between induction method and emotion identified that recall of emotional episodes was specifically associated with activity in anterior insula. As discussed earlier, this region has been suggested to have a crucial role in monitoring internal states, consistent with a role in processing or responding to internally generated emotion. Importantly, this finding provides evidence that recall of emotional and neutral memories involve partly dissociable neural populations. Further evidence for emotion specific processing during episodic memory retrieval comes from the fMRI study of Pfieke et al (2003) who used sentences drawn from pre-scanning interviews to cue subjects to recall positive and negative autobiographical memories. They found that, relative to negative memories, recall of positive memories was associated with activity in right orbitofrontal cortex and temporal pole, as well as bilateral entorhinal cortex, while the opposite contrast revealed activity in right middle temporal gyrus. A similar study by Markowitsch and colleagues (2003) examining only strongly emotional positive and negative memories revealed activity in medial OFC, subgenual cingulate, hippocampus and dorsolateral prefrontal cortex for positive memories with lateral OFC, lateral temporal lobe and cerebellum for negative.

While these findings are interesting, it is difficult to control for aspects of recalled memories, such as vividness and duration, which means that some findings may reflect non-emotional differences between conditions. Other studies have examined

activity associated with retrieval of experimenter-controlled memories in recognition tasks. One issue with these experiments is controlling for the effects of on-line processing of the recognition cues using appropriate contrasts, as we will discuss shortly. Two PET studies have reported activity associated with recognition of pictures drawn from the International Affective Picture System (IAPS), a series of photographic slides of differing emotional impact with standardised ratings of arousal and valence (Greenwald et al, 1989; Lang et al, 1997). The study of Taylor and colleagues (1998) examined blood flow changes during blocks where subjects were either encoding negative or neutral pictures, or judging whether they had seen such images during the subsequent test phase. They found that performing recognition judgements on negative vs. neutral pictures was associated with activity in left ACC, middle frontal gyrus and lingual gyrus. They then compared recognition vs. encoding of negative pictures, as a control for on-line processing effects, and again reported ACC and lingual gyrus activity. They suggested that their findings reflected top down facilitation of early visual processing supporting visual recognition of emotional processing. However, in the absence of differing proportions of target items and no control for different levels of confidence or accuracy between blocks it is difficult to interpret the relationship of these findings to actual retrieval of emotional items.

Dolan et al (2000) explored emotional retrieval using a more elegant 2x2x2 factorial design. Neutral and emotional (both positive and negative) pictures from the IAPS were studied (factor 1) and rated as to their valence. Subsequently these items, together with previously unseen pictures, were employed for one of two tasks (factor 2) – the first of these was a yes/no recognition task, where retrieval of emotional memories was central to the task, and the other involved making indoor/outdoor judgements for each picture, where any retrieval is incidental to the task. Finally

blocks differed as to the proportion of old and new items (factor 3) such that contrasting activity in blocks with high and low proportions of old items allowed a measure of activity related to actual retrieval of emotional memories, rather than simply a cognitive set associated with attempted retrieval. Contrasting activity during emotional and neutral recognition tasks (and subtracting the equivalent contrast for the indoor/outdoor judgement task (in all cases collapsed across target density) revealed activity in the right anterior temporal pole. The interaction of this contrast with target density revealed that a high versus low proportion of targets in the emotional memory condition was associated with activity in the left amygdala. The right temporal pole activation was interpreted as reflecting a cognitive set of emotional memory retrieval, whilst left amygdala effects were suggested to reflect sensitivity to retrieval of emotional memories. This is certainly plausible but, although varying target density is a useful method in separating state and item related effects, which are always an issue in block design studies (see chapter 3), there are still potential confounds in terms of performance and expectancy, especially as the proportion of items in high and low density conditions (80% and 0% respectively) differed so markedly.

Event-related designs allow post-hoc classification of individual trial types on the basis of experimental factors and subject responses, such as whether items are correctly classified as old or new, with time-locked activity across many trials averaged to provide a measure of activity associated with a particular condition (see chapter 3). Maratos and colleagues (2000) used event-related potentials (ERPs) to examine neural activity associated with recognition of negative and neutral words. As discussed in the next chapter, there are characteristic differences in the ERPs associated with correctly classified old and new items, earliest over bilateral frontal

scalp, then left parietal and right frontal regions. Maratos and Rugg (2000) reported that the left parietal and right frontal old/new effects, taken to reflect recollection and post-retrieval monitoring respectively, were smaller in magnitude for negative words. The left parietal differences appeared to reflect greater activity elicited by previously unseen negative vs. neutral words. These findings were interpreted as evidence of 'false recollection' for negative words, and poorer post-retrieval monitoring, reflected in higher false alarms for this item type.

All these studies are interesting in guiding our understanding of emotional retrieval, but all suffer from an important confound of using recognition cues which have inherently different stimulus properties. Although the approaches described above, such as comparing old and new items or activity during retrieval and encoding, certainly ameliorate the confounds of on-line processing, several key problems remain. The first is that the emotional impact of a stimulus may change once it has been experienced. Some items may have less emotional impact on second and subsequent viewings (for example, the 'shock' induced by a gory picture may be diminished by having seen that specific picture previously, or due to general desensitisation through the course of an emotional experiment), whilst others may increase (e.g. where familiarity with a picture may lead to greater concentration on the most significant emotional aspects of the picture). This uncertainty means that contrasts such as above can lead to both false negative and false positive results, in a manner not easy to predict. Secondly, even if emotional impact of old and new items is equivalent, activity in brain regions may not sum in a linear manner, such that memory related activity in structures also associated with on-line processing of emotional stimuli may be masked. Finally, differences may exist between emotional and neutral items which are independent of emotion per se. Emotional stimuli, in

contrast to neutral items, tend to belong to semantically cohesive categories, thus sharing stronger inter-item associations (Phelps *et al*, 1998). They may also be more imageable, but less concrete than their neutral counterparts (Campos et al, 1999). Therefore, a number of confounding elements are present in studies comparing recognition of emotional and neutral items.

One approach to this problem is to examine the neural activity associated with memory for pre-experimentally neutral items which have acquired emotional significance through the course of the experiment. The aformentioned conditioning studies which index this type of activity, are not necessarily dependent on exactly the same processes as those underlying retrieval of emotional episodic memories. An alternative paradigm involves encoding of neutral test items in emotional contexts and examining how this manipulation modulates memory. It has been shown that encoding neutral words in emotional vs. neutral sentences leads to a mnemonic advantage for the former (Phelps et al, 1997). Maratos and colleagues (Maratos and Rugg, 2001; Maratos et al, 2001) adopted this approach for ERP and fMRI studies of emotional retrieval. Neural activity was contrasted between recognition where the word was encoded in an emotional vs. a neutral sentence (e.g. The **bear** lived in the woods vs. The **bear** sank his teeth into the man). In effect, exactly the same kind of test material was presented in each case, and consequently any emotion specific effects could be unequivocally attributed to an influence of emotion on retrieval activity.

In two experiments, Maratos and Rugg (2001) investigated the ERPs associated with the recognition of emotionally neutral words which had been presented in emotionally neutral or negative sentences, as described above. In experiment 1 the test task was old/new recognition. Words encoded in negative sentences elicited larger 'left

parietal' ERP effects than those encoded in neutral sentences and, in addition, elicited a prominent 'right frontal' effect. Since the effects of emotion in this experiment took the form of modulations of old/new effects common to emotional and non-emotional material, Maratos and Rugg (2001) concluded that the findings provided evidence for emotional modulation of memory processing, but no support for the notion that the retrieval of emotional and non-emotional information might engage distinct neural systems.

In their second experiment, Maratos and Rugg (2001) required subjects to make both recognition and source judgements, explicitly discriminating between words which had been encoded in negative vs. neutral sentences. In contrast to the findings of their first experiment, there were now no effects of emotion on either left parietal or right frontal effects, which were large and robust for all correctly recognised words. In light of these findings, Maratos and Rugg (2001) interpreted the results of their first experiment as evidence that contextual information is more likely to be retrieved incidentally, and to capture attention, when it is emotionally valenced. Furthermore, there were subtle differences in the scalp distribution of the activity associated with recollection of emotional and neutral contexts, providing evidence for recruitment of different cognitive processes during retrieval of emotional and neutral memories.

A subsequent fMRI study examined activity elicited during a recognition memory test for words presented at study in the context of negative, neutral or positive sentences (Maratos et al, 2001). Recognition of items encoded in negative vs. neutral sentences elicited increased neural activity in right prefrontal cortex and bilateral medial, superior and anterior temporal regions, including left hippocampus and amygdala. These findings are suggestive of enhanced memory processing and additional emotion-specific processing for items by virtue of their study history. Words encoded

in positive sentences showed increased activity in bilateral orbitofrontal and inferior frontal areas, left anterior and superior temporal lobes, with trends towards effects in the same regions of amygdala and hippocampus as revealed in the negative vs. neutral contrast.

The findings of Maratos and colleagues (Maratos and Rugg, 2001; Maratos et al, 2001) clearly demonstrate that learning an item in an emotional context modified the neural activity associated with retrieval of that item. However, a number of issues remained outstanding. Firstly, the observed effects, particularly in terms of engaging qualitatively different neural populations during retrieval of neutral and emotional memories, were relatively weak and require further characterisation. Secondly, the effects of positive emotional contexts on the electrophysiological correlates of retrieval have not been examined. Thirdly, the effects, if any, of emotional context on retrieval of an item when the context is not recollected have not been determined. Additionally, the effects described previously were all obtained using words as test items, encoding them in neutral and emotional sentences which formed contexts, and of which the test items where an integral part. It is of interest whether such effects hold with different types of test material, and also whether more arbitrary associations between contexts and test items modify the effects of emotional context on retrieval.

This thesis describes a number of experiments aimed at addressing these issues. A non-verbal contextual memory paradigm was developed (described in some detail in chapter 4) using object pictures as test items and photographic scenes, of differing emotional valence, as contexts. Pictorial stimuli are likely to be more effective at engaging emotional processing than verbal stimuli because of their highly concrete nature and 'cognitive immediacy'. The use of pictures to provide emotionally valenced contexts may, therefore, lend greater power to the identification of emotion

effects on retrieval processing than was afforded by the verbal stimuli employed by Maratos and colleagues. Furthermore, the employment of positive as well as negative contexts allows a distinction to be drawn between valence-specific and valence-independent emotion effects, unlike in their ERP experiments.

Chapter 3a: Principles of Functional Neuroimaging

In the 75 years since Berger (1929) recorded electrical activity from the scalp reflecting neural activity in the brain, our understanding of the functioning human brain has been greatly advanced by a number of non-invasive neuroimaging techniques.

These techniques allow the measurement of activity in the functioning human brain, in normal and brain-damaged populations, and provide a complementary approach to neuropsychology in segregating brain regions according to their function. Neuropsychology suffers from several limitations: firstly damage is rarely well circumscribed, and 'hidden' pathology may be present in patients. However, even with an ideal pathological profile, one can only determine the necessity for certain structures remaining intact – detriments in performance may be due to loss of supporting functions, or damage to fibres of passage, in addition to direct involvement of the damaged region in the process being investigated. Finally, reorganisation of the brain may allow relatively spared performance on a task by patients following damage to a structure which is involved in that task in the undamaged brain. Functional imaging, on the other hand, can identify neural activity associated with a particular task, but cannot show the necessity of the activated structure for performance of such a task. In addition to providing information about functional segregation, functional imaging techniques can also be used to inform questions about functional integration, which describes the interactions between different specialised brain areas allowing integrated processing – experiment 6 in this thesis describes an experiment examining functional integration.

Neuroimaging techniques fall into two main categories; firstly the electromagnetic techniques, electroencephalography (EEG) and magnetoencephalography (MEG) measure changes in electrical and magnetic fields respectively, at the scalp. These changes reflect the local field potentials, and associated magnetic fields generated by groups of neurons. Other techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), measure metabolic changes consequent on neural activity. Each of these methods has its own advantages and disadvantages (see table 3.1), but one key issue is the trade-off between spatial and temporal resolution. EEG and MEG have much better temporal resolution than PET and fMRI, whilst the metabolic techniques have better spatial resolution. Therefore, to characterise the neural activity associated with cognitive processes, it is advantageous to obtain information from more than one technique. The data in this thesis was

Characteristics	EEG/MEG	fMRI	PET
Spatial Resolution	Low (~10-50mm)	High (~2-10mm)	High (~6-10mm)
Temporal Resolution	High (~0.01-0.1s)	Low (~1-10s)	V. Low (40-60s)
Relation to neural activity	Direct (LFP)	Indirect (Haemoglobin)	Indirect (Blood flow)
Sampling of activity	Partial and unknown fraction	Near-homogenous	Homogenous
Event-related design possible?	Yes	Yes	No

Table 3.1 Characteristics of electrophysiological and haemodynamic functional imaging measures.

collected using both EEG (high temporal resolution) and fMRI (high spatial resolution).

One important issue in functional imaging is the distinction between 'block' and 'event-related' designs. All EEG data in this thesis was analysed as event-related potentials (ERPs). Averaging segments of the EEG signal which are time-locked to particular events, such as onset of a stimulus, will tend to cancel out noise due to brain activity not time-locked to the event of interest. Waveforms associated with different types of event, categorised either a priori or post hoc, can then be contrasted to isolate patterns relating to specific cognitive processes. Between condition contrasts are easier to interpret and more meaningful than estimations of activity relative to some low-level baseline, where many factors can account for differences in neural activity.

The temporal resolution of fMRI, although much poorer than for ERPs, is also sufficient to allow event-related analysis (unlike PET, which is limited by the half-life of the radionucleotides employed). This is somewhat more complicated than for ERPs, as the haemodynamic response to neural activity is delayed in respect to the event, and therefore the form of the response over time needs to be modelled, and this is discussed later. The ability to use event-related designs is critical in terms of distinguishing between tonic neural activity associated with specific cognitive sets, and phasic neural activity which reflect processing of individual items or events (see Otten *et al*, 2002), and also allows post-hoc classification of individual trials based on factors such as performance. All the experiments in this thesis used designs which were either fully event-related (experiments 1-4) or had a mixed block/event-related design (experiment 5). Note also that the necessity of time-locking the imaging signal, stimuli and cognitive events requires paradigms where onset of events of interest can be tightly controlled – for example in studies of memory retrieval, recognition

paradigms are conducive to imaging investigations, whilst free recall paradigms are not.

ERP Recording and Analysis

There now follows a description of some key issues in ERP research, including principles of electrogenesis, scalp recording, artefacts and pre-processing, and methods of analysis. This review is weighted towards issues important in the current work, whilst wider coverage can be found in Rugg and Coles (1995), Kutas and Dale (1997) and Picton *et al* (2000).

Electrogenesis

An understanding of the neurobiology underlying the signal is fundamental to the interpretation of any imaging result. In the case of ERPs there are two factors to consider – firstly the generation of electrical potentials, and secondly the effective propagation of these signals to the scalp.

In the resting neuron, a potential difference exists between the intracellular and extracellular spaces, such that the opening of ion channels, due either to local potential changes or binding of specific ligands, leads to ionic current flow (principally Na^+, plus K^+ and Ca^{2+}) across the cell membrane, and generates potential differences between locations in the extracellular space. The potential in each region of the membrane reflects the ratio of concentrations of ions in intra and extracellular space.

In the postsynaptic dendrites, graded potentials principally reflect opening of ligand-gated ion channels, and thus transmission of information between neurons, either

excitatory or inhibitory. If a certain threshold of excitation is reached, a series of voltage-gated ion channels in the axon are activated, resulting in an action potential, which does not decay with distance, i.e. it is an all-or-nothing phenomenon. Greater dendritic currents translate to more frequent action potentials, such that intra-neuron communication is coded in terms of magnitude, whilst inter-neuronal transmission is frequency coded. Both types of current may contribute to generating extracellular potentials, though Cooper et al (1980) have shown that dendritic potentials are the main contributor to scalp recorded EEG.

At multiple locations, currents will be flowing either from the intracellular to the extracellular space (a source) or vice versa (a sink). Summation of these individual currents determines the net potential differences within the extracellular space, and the resulting potential is called the local field potential (LFP). However, this field will not simply represent the amount of activity, as both spatial and temporal relationships of the sources and sinks will determine the size of the resultant field (see Kutas and Dale, 1997 for review). Certain configurations of neurons give rise to either 'open' or 'closed' electrical fields. Open field source configurations are those where neurons are arranged such that the sources and sinks of individual neurons are summed without cancelling one another, such that an electrical field can be observed external to that group of neurons. Clearly only groups of neurons with such a configuration can directly influence the EEG recorded at the scalp.

Open field configurations are typical within the neocortex, which has a laminar structure of pyramidal cells, well suited to potential summation (Coles et al, 1986). In contrast, structures not showing such organisation, such as the amygdala, or those where the structural configuration of the laminae is such that they fold back on one another, such as the hippocampus, have closed field source configurations where

electrical potentials cancel one another, preventing external observation of an electrical potential field. A number of different arrangements of neurons can lead to such closed fields, and these are illustrated in figure 3.1. Neurons in these structures will not contribute directly to the scalp-recorded EEG, though note they may still influence it by means of their connections to neocortical structures.

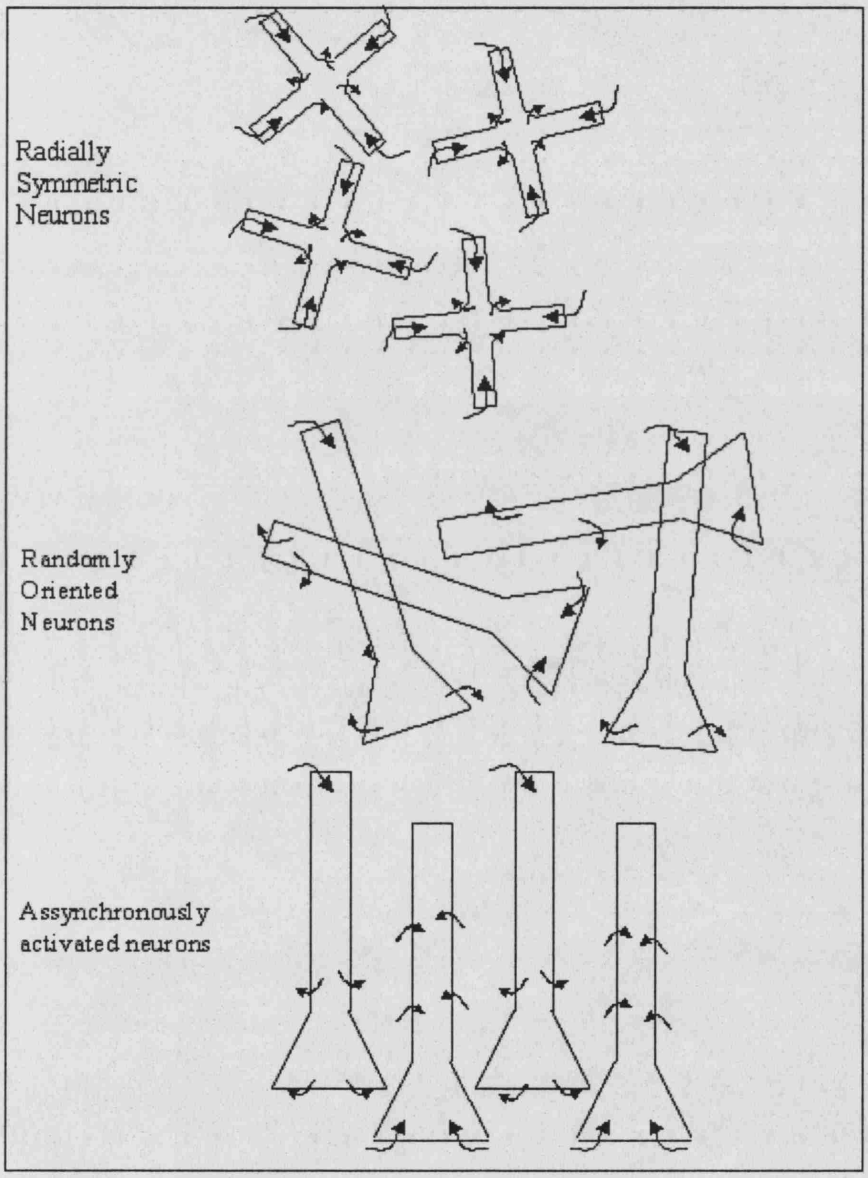

Fig. 3.1 Examples of closed field source configurations (Adapted from Kutas and Dale, 1997)

Even in an appropriate configuration, however, generation of external potential fields require appropriate temporal relationships between neurons. Individual potentials are brief, and are followed by periods of repolarisation, so asynchronously firing neurons may not generate LFPs. One final consideration is the transmission of these potentials to the recording sites at the scalp. Even in synchronously firing, open field neurons the resultant activity must be transmitted though brain tissue, the cerebrospinal fluid (CSF), meninges, skull and scalp, each of which has different conductive properties. Differences in source-scalp distance and the inhomogeneities in conduction preclude effective quantification of the relationship between scalp potentials and neural activity, and result in a biased sampling of neural activity.

In summary, scalp EEG reflects fairly directly the transmission of ionic currents at the neural level, but the considerations of configuration, timing and transmission mean that it does not provide a homogenous measure of all brain activity.

ERP Recording

Electrical activity at the scalp is transmitted to an amplifier through electrodes placed upon the scalp. The placement of electrodes is standardised within experiments, and to some extent across experiments, for comparability of results. Many montages are based on the International Ten-Twenty System (Jaspers, 1958), while manufacturers of electrode placement caps often have montages specific to their products, depending on the number of electrodes utilised.

Increasing the number of electrodes tends to improve the spatial resolution of ERP recordings, but the non-homogenous sampling and limitations of the 'inverse problem' for source localisation (Helmholtz, 1853 cf. Dale and Halgren, 2001) limit

the usefulness of extremely large montages. The signal at each electrode is typically measured with respect to a reference electrode or electrodes. These electrodes are often placed in locations which are minimally influenced by the EEG signal, whilst being subject to similar levels of background noise (see Binnie, 1987). An example of such a location is the mastoid process on each side, and these may be averaged to give a 'linked mastoid' reference. Alternative approaches include referencing each electrode against an average of the activity across all electrodes (average reference) or weighted averages of electrodes surrounding a site of interest (source reference).

Analogue voltage changes are amplified and converted to digital format. The signal is subjected to a band-pass filter, which removes frequencies outside the range of neural activity, reducing the risk of non-physiological artefacts affecting the recorded signal. The high pass filter is set to less than half the frequency of analogue/digital conversion, to prevent aliasing effects, while the low pass filter prevents slow baseline drifts affecting the recording. The digital values of waveform amplitude at each sampling point in time can then be used to recreate the ERP.

Artefacts, Pre-processing and Averaging

The potential differences recorded at each electrode site consist both of the time-locked signal of interest and background noise, which has several components. Each of these components must be minimised in order to maximise the signal-to-noise ratio (SNR), as the signal of interest is typically much smaller than the background noise. The first source of noise is firing of neurons not involved in the process being investigated, due to other ongoing processing, the second is other electrical activity generated by the participant (from eye movements, muscle contraction and ongoing

physiological processes) and the third source is local electrical activity, such as that in the recording equipment.

The impact of local electrical activity is minimised by shielding the participant from electromagnetic fields and earthing them, as well as the aforementioned filtering process, which eliminates electrical activity with frequencies outside the physiological range.

Use of local references should minimise the noise generated by distant physiological events, such as that in the heart, but movement of the eyes, blinking and movement of the muscles of the head will still contribute to the recorded signal. Participants are instructed to minimise their movements, and the electro-oculogram (EOG) may also be recorded concurrently with the ERP to allow monitoring of eye movements.

Eye movements are problematic due to the potential difference across the eye, with the sclera being negatively charged relative to the vitreous humour, causing the eye to act essentially as a dipole, with the positive pole towards the direction of gaze. During a blink, the eyelid acts as a sliding electrode, connecting the anterior pole of the eyeball to the scalp and producing a positive deflection, which is largest at frontal sites and falls off rapidly towards the back of the scalp. In contrast, eye movements themselves cause a positive shift in the direction towards which the eyes move, and a negative shift in the opposite direction, again principally affecting frontal electrodes (see Picton *et al*, 2000).

One approach to dealing with these problems is to use the EOG recordings to exclude trials where vertical or horizontal EOG activity exceeds a certain threshold, to prevent contamination of the average waveform with activity reflecting EOG activity. However, such an approach, particularly if it is stringent, will reduce the number of

trials available for averaging, and hence reduce signal to noise. Another approach is to estimate the contribution of the EOG to the signal at each scalp site, one method for which is described in the following chapter.

After artefact rejection, correction and filtering, individual trials are averaged in order to produce grand average ERPs for each condition. Glaser and Ruchkin (1976) noted that the use of averaging of ERPs to increase SNR depends on three critical assumptions: firstly that the EEG represents a linear sum of signal and noise, secondly that the signal remains the same over trials, and thirdly that the noise is randomly distributed in time relative to the event of interest. Given these assumptions, the averaging of ERPs belonging to each trial type increase the SNR, with greater numbers of trials improving this ratio (noise decreases by a factor of the square root of the number of trials in a condition).

These averaging procedures then reduce the background noise whilst leaving that component of the electrophysiological signal which is time-locked to the event (the evoked activity) unaffected. However, it is worth noting that some brain activity (the induced activity) consequent on cognitive processing is not accurately time locked to the event of interest, and this to will be removed by averaging of waveforms. An alternative to the standard ERP approach is to transform the single-trial information into a frequency form, for example by applying a wavelet transformation. Having done this, individual frequency bands can be extracted and the trials averaged in order to produce time-frequency histograms for each event type, which reveal induced as well as evoked neural activity (see Düzel *et al*, 2003). However, the cost of this approach is that the greater the frequency resolution provided by the transform, the greater the decrease in temporal resolution.

Analysis and Interpretation of ERPs

The analysis and interpretation of ERPs can be approached in several ways, with the type of interpretation pursued by the experimenter influencing the analysis method employed. Without transforming ERP data into a frequency format (see above), three basic methods can be used (often in combination) to investigate ERP effects – analysis of amplitude differences, analysis of scalp distribution of ERP effects, and source localisation.

In order to generate the data for these analyses, average waveforms are generated at each site for each experimental condition. These conditions may be formed by experimental manipulations, be contingent on subject responses, or reflect a combination of the two. As discussed earlier, comparison of waveforms against a pre-stimulus baseline is inappropriate for characterisation due to the intractability of interpretation of such results. Therefore, between condition contrasts within subject and task, chosen so as to differ in the process of interest only, are preferable.

Amplitude Analyses

The ERP waveform can be characterised in terms of amplitude, time and spatial distribution. One way of assessing differences in ERPs is to compare the difference in amplitude between waveforms at particular times and electrode sites. The classical approach to these analyses has been to classify positive and negative deflections in ERP waveforms in terms of characteristic latencies and scalp distributions – for example the P300 describes a positive deflection, with a peak at 300ms, whilst the N400 is a negative deflection, peak at 400ms post-stimulus. The processes being investigated may then be characterised in terms of their effects on specific

components of the ERP. However, such an approach is limited by a number of factors, such as inclusion of timing variations due to experimental and subject factors. More critically, the assignment of functional significance to specific deflections does not appropriately incorporate the multiple components which contribute to these waveforms (see Kutas and Dale, 1997).

An alternative approach to amplitude analysis considers the waveform at different electrode sites within specific time windows or epochs, of a length to give appropriate temporal resolution. Data from multiple electrode sites and epochs can be analysed, and are incorporated as factors within standard statistical analyses, such as analysis of variance (ANOVA). The specific methods employed in this thesis are described in the next chapter.

Topographic Analyses and the Quantitative/Qualitative Distinction

The employment of topographic analyses is an important adjunct to the amplitude analyses described above, particularly in distinguishing between quantitative and qualitative changes in ERPs. Quantitative effects reflect differences in the magnitude of ERPs in different conditions, but no difference in the distribution of waveforms across the scalp. These effects are presumed to reflect changes in the same underlying generators, either in terms of activity level or synchrony (though they may also reflect different probabilities/frequencies of all-or-nothing effects in different experimental conditions; see e.g. Maratos and Rugg, 2001). As discussed previously, the inability of EEG to reflect all brain activity precludes the conclusion that no additional neural populations are active, but qualitative differences do not provide evidence for such effects.

Qualitative effects, however, are concluded from a change in the distribution of ERP waveforms over the scalp. Such changes reflect some form of change in the configuration of the neural generators, such as recruitment of new neural populations, deactivation or desynchronisation of active populations, or change in the relative strength of different neural populations (Johnson, 1995). Qualitative differences provide evidence for differences in the neural states between two conditions, which in turn implies the engagement of distinct cognitive processes (Allan, Wilding and Rugg, 1998). Such a conclusion cannot be drawn from quantitative differences, which can be attributed to the degree of engagement of the same set of processes in each condition. Thus it is clear that amplitude analysis alone is limited in its interpretability. One problem with topographic analyses arises due to the multiplicative (rather than additive) effect of neural activity on scalp voltage. This can lead to spurious interactions between experimental factors and electrode sites which may be due to differences in strength rather than the distribution of generator populations. However, ERP data can be rescaled within each condition, with the aim of removing the confounding effects of magnitude differences on scalp distribution effects (McCarthy and Wood, 1985). This rescaling maintain the relative size of ERP effects at different electrode sites, but removes the differences due to amplitude, allowing condition by site interactions to be interpreted as reflecting differential activation or composition of the underlying neural generators (but see Urbach and Kutas, 2002 for issues with rescaling procedures).

Source Localisation

Given that the patterns of activity in the EEG reflect the overlapping field potentials of different generator populations, one method of analysing data has been to attempt

to determine the sources of activity within the brain contributing to experimental effects. Unfortunately this is complicated by the intractability of the inverse problem in LFP to EEG mapping. The forward problem of determining the scalp distribution of EEG consequent on the activation of a known generator population is well specified, and provides a unique solution. In contrast, determination of the location of a generator from a known scalp distribution is mathematically ill-posed, with an infinite number of possible dipole configurations able to produce a given scalp distribution (Gevins *et al*, 1995; Nunez, 1990). However, by introducing prior constraints upon the source model and selection of the most mathematically parsimonious model, such as by using a weighted minimum norm solution, source localisation can be attempted. As source localisation was not employed in the current work we will not review these in detail here, but will note that there are two main approaches. Equivalent dipole models consider scalp distributions as a function of the locations, orientations and strengths of a (small) number of dipoles, which can be estimated by iteration (see Wood and Allison, 1981). More biologically plausible solutions use distributed source models, which estimate the current distribution across the whole volume of the brain which can contribute to scalp-recorded potentials (see Michel et al, 2001 for review). These distributed inverse solutions provide a blurred image, compared to those generated by dipole models, which both improves their validity, and impairs spatial resolution.

Source localisation may prove a useful tool in ERP analysis, but the inhomogeneity of sampling, distorted transmission of signal and poor spatial resolution mean that currently the information it might provide in addition to classical ERP analyses and haemodynamic measures of activity is limited, and these methods were not employed in the current thesis.

fMRI Measurement and Analysis

We will now discuss the principles of fMRI, and discuss issues of its analysis and interpretation. Wider coverage of MR physics can be found in (Brown and Semelka, 1999), whilst fMRI analysis is covered in more detail in (Frackowiak et al, 2003)

Nuclear Magnetic Resonance (NMR)

fMRI is a special form of magnetic resonance imaging (MRI). Both fMRI and MRI rely on the principle of nuclear magnetic resonance (NMR) (Purcell *et al.*, 1945; Bloch *et al.*, 1946). This technique relies on the measurement of small changes in the energy of protons caused by the change of spin states.

All nuclei possess the quantum characteristic of spin. In nuclei, such as ^1H, with odd numbers of protons, there is a net spin and the positively charged nucleus produces a small magnetic field, such that the nucleus has a magnetic moment. In the absence of external magnetic fields, the orientation of nuclei within a substance is random, and there is no net magnetic field. However, application of an external magnetic field, B_0, causes the protons to align with that field. If nuclei are not perfectly aligned about B_0 then they precess about the field at the Larmor frequency ω_0:

$$\omega_0 = \gamma B_0 / 2\pi$$

where ω_0 is the Larmor frequency in MHz, B_0 is the field strength in Tesla, and γ is the gyromagnetic ratio, a nucleus-dependent constant, in units of $s^{-1} T^{-1}$.

Protons possess energy states dependent on the alignment of their magnetic moment with B_0. When the magnetic moment is aligned with the field, its energy will be lower than when it opposes the field. For the simple spin system of ^1H, the magnetic

moment can have two orientations with respect the magnetic field, either anti-parallel (high energy state) or parallel (low, ground energy state). The amount of energy required to flip states is very low, and individual nuclei will switch between states; in the resting state, however, a greater number will be aligned with B_0 than against it, and net magnetisation will be in positive in the z direction, aligned with the axis of B_0.

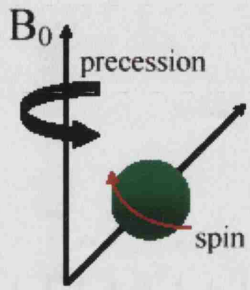

Figure 3.2 Spin and precession of a single proton about the longitudinal magnetization vector B_0.

The spin states of the protons can be excited to the high energy state by application of a radiofrequency pulse B_1 perpendicular to B_0. Energy transfer is most efficient for nuclei with Larmor frequencies equal to the frequency of the RF pulse (e.g. 63.9 MHz for a proton in a field of 1.5 Tesla) such that pulses are designed to excite specific nuclei, most commonly ^1H which has the highest γ, making it most susceptible to external magnetic fields, and is highly abundant in nature. Changing the energy will modify the proportion of nuclei in each spin state, and will therefore rotate the net magnetisation vector. In addition to moving protons to the higher energy state, the radiofrequency (RF) pulse also resets and aligns the phases of the protons. This tilts the net magnetisation vector into the transverse plane.

The net magnetisation rotates about the newly applied RF magnetic field B_1, with the angle from the original equilibrium direction along the *z* axis increasing with exposure time. Varying the amplitude and duration of the RF pulse, allows any desired angle to be produced between B_1 and B_0. For example, if B_1 is applied long enough to equilibrate the aligned and opposite spin populations, the magnetisation vector will be zero and rotated into the *xy* plane. This is referred to as a 90° pulse, producing a 90° rotation of the net magnetisation – a 90° flip angle. For most angles from longitudinal magnetisation (aligned with B_0) there will be a non-zero component of the magnetisation (the transverse magnetisation) in the *xy* plane, which results in the NMR signal.

When the B_1 field is turned off following application of the pulse, the magnetisation vector rotates about B_0 in the *xy* plane, at the spin resonance frequency. The rotating magnetic field induces a current in receiver coils designed to measure the transverse magnetisation. Over time, this signal decreases by free-induction decay (FID) as the protons release the absorbed energy, returning to the equilibrium state, and the net magnetization vector realigns with B_0. This process of relaxation may occur in two ways - firstly energy is given up to neighbouring molecules in the surrounding environment - this is spin-lattice (T1) relaxation, and secondly, energy is given up to nearby nuclei, spin-spin (T2) relaxation.

Spin-lattice or T1-relaxation describes the regrowth of the magnetisation vector along the *z* axis. The time constant T1 describes the exponential realignment with B_0, as protons that have been excited to the higher energy state dissipate this energy to molecules of the surrounding structure ('lattice') as heat. Protons returning to the lower energy state causes regrowth of the magnetisation vector along the *z* axis.

The exact composition of the environment affects T1. For example, the protons in water have a longer T1 than those in fat because the carbon bonds in fat resonate near the Larmor frequency, which facilitates the transfer of energy to the latter. This allows T1 contrast to distinguish between tissues with differing water contents, such as white and grey matter.

In contrast, spin-spin (T2) relaxation describes the loss of coherence of the magnetic moment in the *xy* plane (the transverse magnetisation, Mxy). This occurs as neighbouring spins pass energy from one to another, resulting in desynchronisation of spins. Their slightly different rotation frequencies result in phase differences that gradually decrease Mxy. The decrease of Mxy will always be faster than the longitudinal relaxation (T2<T1) as two mechanisms for magnetic cancellation are operating.

Additional dephasing will occur if the applied magnetic field environment is non-uniform. In a non-uniform field, spins in different parts of the object will be rotating at different frequencies and quickly lose coherence (become dephased), the object then possessing less net transverse magnetisation because of the resulting cancellation. This loss of transverse magnetisation due to inhomogeneous fields is often much shorter than the natural T2 signal decay and is characterised by another exponential time constant, T2'. The value of this time constant is determined both by the technical implementation of the magnetic field and any field inhomogeneity caused by the properties of the object itself. $T2^*$ relaxation reflects the combination of T2 and T2' signal decays, and fMRI often employs sequences weighted towards $T2^*$. These local inhomogeneities are of great use in functional imaging, as we shall describe later, but are also problematic, causing image distortions and signal loss. The contributions of static sources of inhomogeneity (such as B_0 inhomogeneity, resulting from

imperfections in the structure of the magnet) can be reduced, or even eliminated, by use of 'echoes'. One form of echo which can be induced is a spin echo, where a 180° pulse is applied at some time *t* after the initial (typically 90°) excitation pulse. This 180° 'echo' pulse excites spin phases towards realignment and the signal becomes greater until time 2*t* when all spins again have the same phase and Mxy is again at a maximum. The time 2*t* is called the echo time (TE). An alternative means of generating echoes employs magnetic field gradients to dephase and then rephase the spins. Adjusting the time of the dephase/rephase gradient balance allows the time of echo formation to be changed. 'Gradient echo' sequences are often employed for rapid imaging, as they can produce faster echoes and use less RF power than sequences generating spin echoes.

Localisation of NMR Signal and Image Formation

The preceding account details the generation of the MR signal, but for a sample in a uniform magnetic field it is not possible to differentiate spatial locations within that sample. Application of a second magnetic field which varies in strength along an axis of the object (the gradient field) leads to variations in the spin resonance frequencies of protons at different locations within the material (as ω_0 is directly proportional to field strength, according to the Larmor equation). This has two applications – firstly the brief application of a gradient at the time of the RF pulse allows the excitation of a particular slice of the sample, the characteristics of which are determined by the frequency and bandwidth of the pulse. This allows a slice-by-slice investigation of the sample by selective excitation. Secondly, in a stable gradient field, the number of spins resonating at a particular frequency determines the amplitude of that frequency in a spectrum of observable resonance frequencies. For each frequency component of

the measured signal, the known value of the applied gradient strength and direction can be used to calculate the position from which the signal came, allowing frequency coding along one axis.

In order to reconstruct a two dimensional image of spin densities in each slice, coding along a further axis is required, and the phase of proton spins can be utilised for this. Induction of location-dependent phase results from temporary application of a linear gradient perpendicular to the main gradient field. This increases the transverse dephasing of proton spins as local magnetisation vectors rotate with different frequencies depending on their positions within the phase gradient. Along the axis of this gradient position-dependent phase differences are observed among the magnetisation vectors. The degree of dephasing is dependent upon the length of exposure to this gradient field, such that a series of increasing gradient pulse lengths enables a reconstruction of the frequencies giving rise to the dephasing of transverse magnetisation. Using this technique, the amplitudes of spin frequencies can be determined and expressed as a spin density projection along the phase encoding axis.

Together the use of selective excitation and positional coding using both frequency and phase allow signal localisation in three dimensions. Applying the gradients step-wise results in the division of the sample into cuboid volume elements or voxels, the sizes of which depend on the step-size in the gradients and the width of the RF excitation pulse. Within one voxel, all protons have the same spin and phase encoding, with the signal from that voxel being the sum of spin contributions from all protons. Increasing voxel size improves the SNR in the voxel, but leads to other difficulties such as increasing susceptibility to artefacts near tissue boundaries (e.g. Wadghiri et al, 2001) and increased risk of including groups of protons with very

different behaviour (partial volume effects; see Brown and Semelka, 1999). Choice of voxel size also, of course, limits the maximum spatial resolution of the imaging.

BOLD Contrast and fMRI Sequences

As discussed previously, the MR signal is affected by local magnetic inhomogeneities. Haemoglobin (Hb), the protein in blood which transports oxygen, has different magnetic properties depending on whether or not it is carrying oxygen. When no oxygen is bound, the iron component of Hb contains 4 unpaired electrons, giving the haem group a net magnetic moment (Pauling and Coryell, 1936). In the oxygenated state, this net moment disappears as the unpaired electrons are redistributed between iron and oxygen. The magnetic state of blood therefore reflects its level of oxygenation.

The ratio of deoxygenated to oxygenated Hb within a particular voxel is reflected by the field inhomogeneity induced by local field gradients. In particular, the increased dephasing of spins leads to loss of transverse magnetisation and a decrease in the $T2^*$ relaxation time. This effect was demonstrated in animals by Ogawa and colleagues (Ogawa and Lee, 1990; Ogawa *et al.*, 1990) and Turner and colleagues (1991). Experimental manipulation of the Hb/HbO ratio produced detectable changes in a $T2^*$-weighted sequence both in blood vessels and, critically, within the tissue water surrounding them. This signal difference was found to be sufficient to act as a contrast source in humans (Ogawa *et al*, 1992; Kwong *et al*, 1992) and named Blood-Oxygen Level Dependent (BOLD) contrast.

These changes in BOLD reflect the underlying activity in the brain (the nature of this relationship will be discussed shortly), but in order to effectively image the

functioning brain there are two important requirements. Firstly, the contribution of BOLD to the imaging signal must be sufficient. This is achieved by weighting the sequence towards $T2^*$ contrast by using longer repetition time (TR; the time taken to acquire each image volume) and TE. Secondly, the speed of MRI acquisition must be sufficient to track dynamic processes. Spin-echo sequences, often used for structural imaging, can take minutes to acquire each volume, which is clearly too long for event-related functional imaging. More rapid acquisition methods have been developed, and the principal one used for functional imaging is echo-planar imaging (EPI; Mansfield, 1977).

EPI sequences employ very rapid gradient reversals to create multiple gradient echoes. This allows for a greater sampling of *k*-space, the two-dimensional frequency space in which MR data is represented following Fourier transformation (which converts the data from the time to the frequency domain). Most MR sequences sample a single line of *k*-space after each RF excitation, whereas EPI sequences can sample the whole of *k*-space after each pulse.

Coupling of Neural Activity and Blood Oxygenation

One issue crucial to the understanding of fMRI, and its relation to other measures of brain function such as EEG, is the nature of the coupling between the BOLD response and the underlying neural activity. This issue is still contentious, and for a wider review than presented here see Arthurs and Boniface (2002). Regional changes in blood flow (and therefore Hb) are due to the vasodilatory influence of products of metabolism. At rest, neuronal firing per se only accounts for ~3% of cerebral metabolic demand (Creutzfeld, 2002), and as such is not a major contributor to

changes in flow. Most of the energy demands arise at synapses due to breakdown, reuptake and synthesis of neurotransmitters, as well as regulation of ionic gradients. This means that blood flow is modulated by subthreshold as well as suprathreshold activity, which has resonance with EEG being principally due to dendritic potentials. It also means that the metabolic demand at a region may be principally dependent on the spike activity of afferent fibres, which may have cell bodies quite distant from the site of metabolic changes. Another much debated (and unresolved) issue is the contribution of inhibitory firing to the BOLD signal – energy is certainly required at inhibitory as well as excitatory synapses, yet such activity will decrease LFPs around the dendrites, such that disparate changes would be observed with fMRI and EEG/MEG. The significance of this inhibitory contribution is still debated (see Raichle, 1987; Heeger *et al*, 1999; Waldvogel *et al*, 2000) but identifies another reason for differing sensitivities of haemodynamic and electromagnetic imaging methods. However, it is accepted that the BOLD signal does reflect neuronal activity in some sense (the details of modelling the haemodynamic response to neural activity is discussed later) and, in human visual cortex at least, is approximately proportional to the aggregate firing rate of neurons in the same region (Heeger *et al*, 2000; Rees *et al*, 2000).

We have discussed so far the principles of BOLD fMRI, and will now go on to describe the methods adopted here for preprocessing and analysis of such data.

Analysis of fMRI data

The principal use of fMRI is to detect regionally-specific differences in the brain activity associated with particular processes or states, and on the basis of these to infer

functional specialisation of these brain regions. Additionally it can be used to investigate functional integration, that is the integration of different specialised brain regions to perform particular processes, and a method for investigating such connectivity is described in a later chapter.

In order to draw regionally-specific inferences the data must conform to a standard anatomical space and the transformation of data to this space requires several steps. The imaging time series is first realigned to a common reference frame to correct for subject movement during scanning. This process also calculates subject movements over time, which induce artefacts in the signal, so that they can be accounted for either by attempting to unwarp the images themselves, or by including the parameters as regressors when estimating the effects of experimental manipulations. Due to the slice-wise nature of data collection, different slices are scanned at different times, and these slice-timing differences can also be corrected. The data are then transformed using linear and nonlinear mappings into a standard anatomical space (Friston *et al.*, 1995). This normalisation procedure allows for averaging across subjects and places the data within a standardised co-ordinate system, allowing comparison with other studies. The data can then be smoothed and entered into a statistical model in order to form inferences. The specific methods used in this thesis are described in the following chapter.

Characterisation of Haemodynamic Responses

Following preprocessing, the imaging data collected conforms to a standard format. The next stage is to set up the statistical model to test for differences between conditions. In contrast to ERP analysis, where the data pertaining to each trial is

discrete, the relatively long latency of haemodynamic responses mean that event-related fMRI studies must model the expected responses over time following an event of interest. Fortunately, so long as events are not spaced too closely, the evoked haemodynamic responses sum in approximately linear fashion (non-linearities due to saturation, believed to arise in the mapping from blood flow to BOLD signal, may be present with stimulus-onset asynchrony (SOA) of less than 8s, but such effects are small down to SOAs of approximately 2s; Miezin et al, 2000). Therefore, events can be modelled as discrete delta functions, with onset times linked to timing of the scans, and the expected contribution of that event to the haemodynamic activity at scan *t* afterwards determined by convolution of the delta functions with one or more basis functions which model the haemodynamic response. Multiple basis functions may be employed in conjunction, in order to characterise the response, and to allow sensitivity to responses of different forms. Very general basis sets can be employed, such as Fourier sets and Finite Impulse Response (FIR) sets, which make minimal assumptions about the shape of the response, and use linear combinations of either (short) boxcar or sine and cosine basis functions to describe the data. However, in order to model the haemodynamic response effectively, these basis sets typically employ a considerable number of basis functions, which reduces the degrees of freedom available to describe designed perturbations, and thus weakens the ability to detect experimental effects. More parsimonious basis sets can be generated by making various assumptions about the response shape, for example using a combination of gamma functions informed by well characterised empirical data. One example of this is the 'canonical haemodynamic response function (HRF)'. This 'typical' BOLD impulse response is characterised by 2 gamma functions (one modelling the peak, and the other describing the undershoot of the response) with timing based upon principal

component analysis of a well characterised data set (Friston et al, 1998). Such basis functions may be complemented by their partial derivatives, for example with respect to time or dispersion, to improve the ability to detect responses with different latencies or duration of peak response. After application of the appropriate model, a low pass filter may also be applied in order to prevent artefacts from slow phenomena, such as scanner drift or aliased biorhythms, similar in principle to application of filter to EEG as described earlier.

The estimates of activity in different brain regions under different conditions can then be analysed in a number of different ways, each with their own assumptions, advantages and disadvantages. It is beyond the scope of this thesis to compare various methods of fMRI data analysis, and all the functional segregation analyses were based upon a single technique, statistical parametric mapping (SPM), described in chapter 3b.

Inference in fMRI

Following estimation of parameters and statistical evaluation, inferences can be drawn from the resulting statistics. Two important issues, selection of between-condition contrasts appropriate to the investigated process and the link between neural activity and the BOLD signal, have already been discussed. It is also important to distinguish between subject and population level inference, and appropriate control of type 1 error, given the large number of comparisons in typical fMRI studies.

One approach to fMRI inference considers each observation in each subject scanned to be independent, such that the final model will (before correction) have one degree of freedom per observation. Such 'fixed effects' models allow inferences to be drawn

only about the neural activity of the particular group of subjects at the time of scanning. They are associated with high degrees of freedom, which lends considerable statistical power, and only a small number of subjects are typically required when using such an approach. A significant danger with this type of analysis is that observed effects can be driven by strong effects in some subjects which are absent in others. This can be protected against by performing conjunction analysis amongst the subject group, such that only effects which are significant in all subjects are revealed. Such an approach is equivalent to a series of replications of a case report on an individual subject, such as are typically employed in neuropsychological studies.

An alternative approach is to use a 'random effects' model (see Penny and Holmes, 2003) where, for each specified contrast, one contrast estimate per subject (taken from the 'first level', within subject model) is entered into the 'second level' statistical model, and between subject variance used to calculate t- or F-statistics. Due to the consideration of between subject variability, this approach allows inferences to be made about the population from which the subjects were drawn, unbiased by strong effects in a subset of participants. Random effects models have only one degree of freedom per subject, far fewer than for an equivalent fixed effects analysis, and so considerably more subjects are required (12 probably being the minimum acceptable).

The issue of controlling type 1 error is an important one in fMRI because a large number of voxels are tested for significant effects, and at standard statistical thresholds (i.e. $p<0.05$) a considerable number of significant differences would be expected to occur by chance. Two basic approaches can be applied for control of these error – either correction for multiple comparisons (such as Bonferroni correction) can be applied, or a much more stringent statistical threshold than normal can be

applied, sometimes with the additional application of a spatial extent threshold (so only effects which occur in at least a certain number of contiguous voxels are reported). The correction of p values for multiple comparisons in fMRI is based on Gaussian field theory, which accounts for the fact that data in adjacent voxels are not independent due to spatial smoothing in the original EPI images, and is less stringent than a Bonferroni correction for smooth data. The degree of correction is dependent upon the volume to which the correction is applied, such that in the absence of anatomical constraints on the experimental hypothesis, the volume of the whole brain is used for correction. Where there are *a priori* anatomical predictions, specific tests for significance within the hypothesised regions need only be corrected for the volume of each region (this is known as small volume correction).

However, correction for 'family-wise error', which at a threshold of $p<0.05$ aims to restrict the chance of any type 1 error within the experiment to less than a probability of 0.05 based on the expected Euler characteristics of the data, applies an excessively stringent correction in studies with few degrees of freedom. As experiments employing random effects approaches, as those presented in this thesis, typically have few degrees of freedom, such correction can be excessively conservative. Nonetheless, it is crucial to protect against false positive results, and as such the statistical thresholds applied to data uncorrected for multiple comparisons must be sufficiently stringent to perform this role. For example, many studies use a minimum significance level of $p<0.001$ (i.e. 50 times more stringent than the 'standard' statistical threshold) and may also apply a 'spatial extent threshold' such that a minimum number of spatially contiguous voxels must exceed the threshold for any to be regarded as significant. This improves the chance that effects have some physiological relevance.

Summary of Functional Neuroimaging

The present chapter has discussed the principles and application of ERPs and fMRI as techniques for imaging brain activity, and how this can provide meaningful information about the correlation of this activity with cognitive processing. The constraints and sensitivities of these techniques, outlined above, must be considered during experimental design, implementation, analysis and interpretation of functional neuroimaging data. The details of the protocols employed in this thesis are detailed in chapter 3b.

Chapter 3b: General Methods

This section is concerned with describing some of the methodological features which were common across multiple experiments described in this thesis. Firstly the selection of materials and the development of the encoding paradigm, which was essentially the same across experiments, and their validation, are described. There follows a discussion on the general approach taken for processing and analysis of ERP and fMRI data.

Materials

The first aspect of experimental design described here was the selection and validation of materials for the paradigm. As described in chapter 2, one aim of this thesis was to develop a pictorial contextual memory paradigm, which required both selection of appropriate pictures to form positive, negative and neutral contexts, and the selection of critical stimuli which were pre-experimentally neutral.

The contexts were drawn principally from the International Affective Pictorial System (IAPS; Lang et al, 1997), a series of photographic slides with standardised valence and arousal ratings, which have been widely employed in emotional research. Initially these were categorised based upon the normative ratings supplied into neutrally (Valence range), negatively (valence range) and positively (valence range) valenced contexts. Any pictures which were not within the specified range, or showed a standard deviation of more than 0.75 in their valence ratings were not considered for materials. Some additional photographic material was also selected to

supplement the IAPS pictures, and constituted about 5% of the set from which the final contexts were selected.

As emotional responses are influenced by cultural factors (e.g. Jenkins and Karno, 1992) the categorised photographs were then rated for valence and arousal by 12 British subjects (6 female, mean age 23years) to obviate possible differences with the American subjects on which normative ratings were based. These subjects rated valence and arousal separately for each photograph, using 5 point Likert scales. The mean and standard deviations attributed to each photograph are reported in the appendices, along with normative ratings for those drawn from the IAPS. New criteria were applied for categorisation, such that neutral contexts had mean valence ratings between 2.5 and 3.5, positive contexts had valence ratings greater than 4 and negative contexts less than 2. Additionally, to reduce inter-subject variability in responses to particular stimuli, pictures with SD of greater than 0.75 in valence ratings was discarded. None of the material used was sexual, as responses to such material may be particularly variable, and because of slide-specific differences in responses of male and female participants. For the majority of the experiments described in this thesis 180 photographs (60 each neutral, positive and negative in valence) were used as experimental contexts, together with additional pictures for filler items early in each imaging run (items not employed in contrasts, which allow stabilisation of brain responses to the stimuli) and as examples for pretraining.

The critical objects were taken from a pool of 400 pictures, presented within a yellow square so as to allow segregation from background contexts when superimposed upon them (described later). These objects came from a wide range of semantic categories (e.g. furniture, cutlery, ornaments, sporting equipment) and were chosen so as to be free of strong emotional associations. The same group of subjects which rated the

backgrounds also rated the objects, and those which deviated from neutral valence (mean rating < 2 or > 4 or SD < 0.75) or were arousing (mean > 2) were discarded. 360 items were selected as critical stimuli, together with additional filler and training items.

The next step was to organise the pairing of contexts and objects. For experiments 1-4, the selected stimuli were used to form six study lists. Each list included the 180 emotional and neutral contexts, arranged pseudorandomly, with no more than three pictures from the same valence category presented consecutively. Each critical object was paired with a neutral background in one list, a negative background in another, a positive background in a third, and was available as a new item (for the associated test lists) for the remaining three study lists. The first two background/object pairs in each part were neutral filler items. Therefore each study list consisted of 186 background /object pairs (including the fillers). A practice study list of 6 background/object pairs was used to train subjects prior to the experiment proper.

Study Phase Design

Although the nature of the memory test was altered between experiments, in order to investigate different questions about retrieval processing, the form of the study phase remained largely constant throughout. The aim of this phase was for subjects to encode the neutral critical objects, in association with the contexts. Given that our power to detect the influence of emotional context on retrieval processing would rely on the number of trials in each critical condition (see Chapter 3), it was important that subjects would be able to recognise a large proportion of studied items. Given that any effects of emotion might depend on the ability to recollect emotional associations

of test items, it was also important that subjects recollected these associations on a reasonable proportion of trials.

A number of aspects of the encoding task design were manipulated, and each configuration tested for suitability. A number of pilot subjects undertook different encoding tasks and were tested on recognition memory (categorise items according to whether they were seen during the preceding study phase (old items) or whether they are being viewed for the first time (new items)) and, for old items, source memory for the emotional context (categorise items according to whether they were previously encountered in a neutral, negative or positive context).

The design chosen on the basis of these pilot studies, and used throughout this thesis, began with the presentation of the background context alone for a period of 3s. In most cases subjects either verbally rated the valence of the context, using a Likert scale, (Experiments 1, 2 and 4) or categorised the context as being negative, neutral or positive (Experiments 3 and 5). The critical object, within its yellow box, was then superimposed upon the background context. Subjects then performed an associative task, generating an arbitrary connection between the background and the object. For example, presentation of a picture of a pen with a context of someone at work might lead the subject to imagine that the pen was on the desk pictured, whilst the same pen with a context of a body in a morgue could be considered as the pen used to sign the death certificate, or it could be a gift in a context showing a group of happy people together.

Six pilot subjects who undertook this encoding task showed, during a subsequent test phase, a mean (SD) correct recognition of old items of 83%(5.6) on a test list consisting of the 186 old objects, and 90 new objects. False alarms (i.e. new items incorrectly classified as old) were low (9.2%(4.2)). Items categorised as old were

further distinguished by a forced-choice source memory judgement as to whether each item had been paired with a neutral, negative or positive background at study. This showed a mean source accuracy of 63%(8.4), collapsed across valence. These pilot results suggested that the study design did indeed produce sufficient memory, both for objects and contexts, for the planned experiments.

All stimuli were presented using Cogent 2000 (Wellcome Department of Functional Imaging, http://www.fil.ion.ucl.ac.uk), a toolbox for MATLAB (Mathworks Inc., www. mathworks.com) which allows presentation of visual and auditory stimuli tightly time-locked to a serial port trigger, which can be used to synchronise timing between the cognitive interface and recorded functional imaging signals.

General ERP Protocol

We will now describe the general protocol adopted for all ERP experiments described in this thesis. Where individual experimental factors differed from this, it is noted in the relevant chapter.

EEG was recorded from 31 Ag/AgCl electrodes. Twenty-nine of these were embedded in an elasticated cap (Falk Minow Services 'Easycap', http://www.easycap.de/easycap; Montage depicted in Fig. 3.3) and one was attached to each mastoid process. Recordings were made with reference to Fz and subsequently re-referenced to linked mastoids. Vertical and horizontal EOG were recorded from electrode pairs above and below the right eye and on the lateral canthi. EEG and EOG were amplified with a bandwidth of 0.03-30Hz (3 dB points) and digitised (12 bit) at a rate of 125Hz.

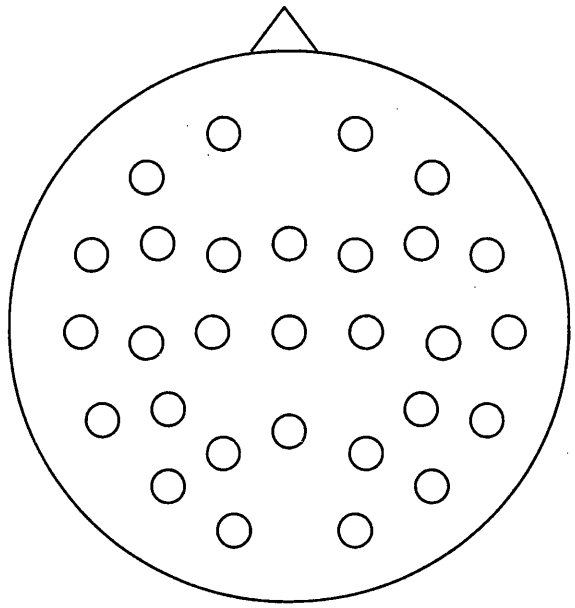

Figure 3.3 Montage showing the 29 electrode sites used to form ERPs.

Prior to placement of the electrodes, each site was cleaned and slightly abraided, to reduce electrical impedance. Electrode placement was followed by insertion of conductive gel between the electrode and the scalp, to improve electrical contact. These measures reduced the influence of potential artefacts arising from local electrical activity on the recorded signal.

EEG recordings were divided into recording epochs which began 104ms prior to stimulus onset with duration of 2048ms. A correction procedure was used to minimise the number of trials rejected due to blink artefacts. The contribution of the EOG to the signal at each scalp site was determined using linear regression (see Willis, 2000), and the estimate subtracted from the EEG (see Jervis *et al*, 1988; 1989). Although using such methods for eye movement artefact can be inaccurate, particularly due to contamination of the EOG signal by EEG (see Picton *et al*, 2000) it works well for blink correction, and is used by many researchers in conjunction with rejection of trials showing large artefacts. Trials containing non-blink vertical eye movements or horizontal eye movements were rejected, as were those where A/D

saturation occurred or baseline drift exceeded ±40μV. ERPs were formed for each condition of interest, with subjects excluded from further analysis if the number of trials contributing to any waveform of experimental interest fell below 16 trials. Waveforms were digitally smoothed with a zero-phase shift low pass filter (3dB down at 19.4Hz).

Between condition comparisons were analysed across multiple subjects, incorporating amplitudes into repeated-measures ANOVAs, with subjects treated as random effects i.e. subjects are treated as being randomly drawn from a population, such that inferences can be made about that population (see Penny and Holmes, 2003), with n-1 degrees of freedom from n subjects. One important issue with the use of parametric statistics for ERP analysis is the violation of sphericity - for example the covariance between proximal electrode sites is likely to be greater than for those further apart. The ANOVA is robust to small violations of parametric assumptions, but non-sphericity was further corrected for by application of the Greenhouse-Geisser procedure. This technique estimates the degree of non-sphericity associated with a contrast, and reduces the degrees of freedom accordingly (Keselman and Rogan, 1980). The factors employed in particular ANOVAs are described in the relevant chapters. Topographic analyses were carried out on difference waveforms rescaled using a minimum/maximum scaling procedure, so that differences in topography could be asserted as reflecting different configurations of neural generators (see chapter 3a). It should be noted that the use of difference waveforms and min/max, rather than root-mean-squared (RMS) scaling obviates the concerns raised by Urbach and Kutas (2002) about rescaling artefacts.

General fMRI Protocol

All MRI data acquired in this thesis were acquired from a 1.5T Siemens SONATA whole body scanner (Siemens, Erlangen, Germany). RF pulses were transmitted via the body coil, while FID signal was detected with a separate head coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD (blood oxygenation level dependent) contrast. Repetition times (TR) varied across experiments, but all were offset relative to the SOA of each experiment so as to give an effective sampling rate of approximately 2Hz.

Data were acquired during multiple sessions (two each at study and test) with the first five volumes of each session discarded to allow for T1 equilibration effects. Preprocessing and analysis of images were all performed using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, UK; Friston et al, 1995), as described below.

Preprocessing

The acquired images were first realigned in space. Whilst head motion during scanning was minimised by immobilising the head with padding, some movement is inevitable. This movement means that volumes acquired at different times may not be perfectly aligned, and furthermore the change of position within the B_0 field will lead to artefactual changes in signal intensity. Realignment proceeded by estimation of 6 parameters describing the affine 'rigid body' transformation that minimises the sum of squared differences between each volume and the first. These parameters describe three translations along and three rotations about orthogonal axes. These parameters were then used to perform the transformation by resampling the data using trilinear

interpolation. In addition the changes in intensity due to movement relative to B_0 were either modelled as potentially confounding covariates in the design matrix (chapters 5 and 7) or used, in conjunction with scans 'mapping' the B_0 field to apply an unwarping transformation on the images (chapter 8). These methods aimed to remove movement-related variance from the time series which would otherwise be attributable to error (decreasing sensitivity) or, if movement is correlated with the task, to evoked effects.

For the experiments described in chapters 5 and 7, we also corrected for differences in the time of acquisition for slices within a given volume. Due to stimulus onset times being specified relative to the acquired volume (with the model assuming all slices within a volume are acquired simultaneously), and the fact that slices within any given scan are acquired sequentially, different slices within each volume may show greater sensitivity to the haemodynamic model employed. Slice-timing correction corrects the data for each volume such that the data from each slice correspond to a single time point (typically the middle slice). This is achieved by sinc interpolation of the data over time.

The above steps essentially standardised the data within each subject, but for inferences across subjects, and for ease of comparison between experiments and laboratories, the data was then mapped onto a standard anatomical space (in this case the space defined by the atlas of Talairach and Tournoux, 1988). In order to perform this step, we estimated the parameters describing the warp needed to map an image from each subject (using a mean image formed during realignment) with a template EPI image. Two sets of parameters, one describing a 12-parameter affine transformation (similar to that used during realignment, but additionally accounting for zooms and shears), and the other a discrete cosine set of basis functions, were

estimated within a Bayesian framework. The deformation described by these parameters is updated iteratively to minimise the sum of squared differences between the deformed image and the template, i.e. the chosen deformation is that with the highest probability of generating the template image from images of individual subjects. As we have prior knowledge about the likelihood of given transformations, the estimation can be improved by weighting the contributions to least squares of the parameters (Ashburner *et al*, 1997).

After normalisation, the fMRI data were 'smoothed' by application of a Gaussian kernel of known width (the present experiments all used kernels with full width half maximum (FWHM) of 8mm in each dimension), to each voxel, such that the signal ascribed to each reflects a weighted average of local BOLD signal. One reason for this smoothing is that, even after normalisation, small differences exist in functional anatomy across subjects. Appropriate smoothing means that effects are expressed at an appropriate spatial scale for functional anatomy to be near-homologous across subjects. Smoothing also causes the data to be distributed more parametrically, ensuring validity of our statistical tests.

SPM Analysis

Following preprocessing, BOLD responses were characterised using a haemodynamic basis set, as described in chapter 3a. In all the fMRI experiments in this thesis, we employed a basis set of the canonical HRF together with its partial derivatives with respect to time and dispersion (although some analyses are based upon the canonical HRF alone where this was found to be primarily responsible for observed effects, in order to simplify inference). We then performed statistical analysis of evoked

haemodynamic responses to test for experimentally-induced effects at each intracerebral voxel individually and simultaneously. Use of a general linear model (GLM) for mass univariate analysis allows calculation of t and F statistics, based on estimates of the parameters reflecting the contribution of different experimental effects to the observed signal. This procedure allows formation of an 'image' of statistics (i.e. SPM).

The GLM describes variation in the data, Y, in terms of a linear combination of explanatory variables, plus an error term. Its input can be visualised as a 'design matrix' with one row per observation (i.e. acquired EPI image) and one column per model parameter. Since the number of parameters is typically fewer than the number of observations, there is no exact solution (the model is overdetermined) and therefore the parameters that best fit the data were estimated, by applying a 'least squares' procedure.

However, in general, fMRI data do not have residuals which are independent, identical and normally distributed, as the GLM assumes. As the duration of the haemodynamic response is typically longer than the time between observations, there are temporal autocorrelations between error terms. One way in which this can be corrected for is by application of a known temporal smoothing function to the time-series, and appropriate adjustments of the estimators and degrees of freedom (Friston and Worsley, 1995). This method, however, may produce less efficient estimators due to the removal of high frequency components, which may contain signal. An alternative approach is to estimate the intrinsic autocorrelation in the data, and use this to create a filter which 'pre-whitens' the data before application of the GLM. We used such a method for estimating autocorrelation, using first order autoregression (an AR(1) model) estimated from the covariance of the data. These estimates were used to

create a pre-whitening data filter which was applied to the data, and the GLM refitted. SPM repeated this process iteratively until the residual errors are white (i.e. resemble 'white noise', with equal power in all frequencies).

Relative to AR(1) methods which pre-whiten data on the basis of residuals (see Bullmore et al, 1996), this technique reduces potential bias arising from correlation in the residuals after removing modelled effects (see Friston et al, 2002; Henson, 2003). It does, however, induce potential bias resulting from the signal, and drifts in the data. Furthermore, inefficient estimation may arise from variability in autocorrelation over voxels (see Woolrich et al, 2001). The version of SPM used for the experiments in this thesis pools over voxels when estimating the AR(1) parameters, and assumes that the ratio of hyperparameters describing the autocorrelation is stationary over voxels. A single voxel-specific scaling factor is then used to ameliorate anatomical variability and provide efficient estimation of the appropriate adjustment of degrees of freedom.

The generalised least squares solution on the whitened data provides estimates of the contribution of each of the experimental (e.g. conditions) and confounding (e.g. head movement) variables to the variance in the data. This allowed calculation of subject specific contrasts between conditions. For inference, these estimates were then used in a random effects model (see chapter 3a), such that inferences can be generalised to the population, rather than just the scanned subjects. Additionally this approach makes our ERP and fMRI results more comparable. In order to control for false positives a strict threshold of $p<0.001$ (i.e. 50 times more stringent than the 'standard' statistical threshold) was applied to statistical tests. In addition, a spatial extend threshold of at least 5 contiguous voxels ($k=5$) was applied to all tests of 'simple effects' (i.e. direct contrast between 2 conditions, without interaction terms), as statistically robust effects across tests applied to a number of voxels within a specific

brain region increase confidence in the correlation between BOLD signal in that region and the effect of interest. Since our sensitivity to detection of interactions is less than that for simple effects, the spatial extent threshold was not applied to these tests, to reduce the risk of false negative results.

Chapter 4: Event-Related Potential Correlates of the Incidental Retrieval of Emotional Context

Introduction

As discussed in chapter 2, memory is often enhanced for events or items which are emotionally significant, and the cognitive and neural mechanisms responsible for interactions between memory and emotion are of interest. One influential hypothesis is that the primary locus of these interactions is during consolidation of memories (Adolphs et al, 2000; Cahill and McGaugh, 1998; Tabert et al, 2001). By this argument, the enhancing effects of emotion on memory emerge over time to render emotional memories more durable or accessible than non-emotional memories. The mechanisms underlying the retrieval of the emotional and non-emotional memories could, however, be equivalent. Alternatively, additional to any effects at encoding and consolidation, emotion may also influence retrieval processes (Dolan et al. 2000; Maratos et al., 2001).

A few studies have investigated emotional retrieval processing using functional imaging methods (see chapter 2), though a considerable number of outstanding issues remain. One question of interest is whether emotion modulates the actual retrieval of information from memory, or subsequent processing of retrieved information. The majority of previous studies of emotional retrieval have employed haemodynamic measures of neural activity which, even in relatively rapid event-related designs, lack the temporal resolution to accurately determine the time course of item-related memory effects, and hence resolve this question (see chapter 3a).

ERPs provide an alternative method for investigating the neural correlates of emotion vs. emotional memory retrieval. Although lacking the spatial resolution of haemodynamic methods, ERPs have the benefit of high temporal resolution, and are thus well suited to examining the time-course of the effects of interest (chapter 3a). Specifically, it can be determined at what time any modulations of neural activity resulting from retrieval of emotional vs. neutral information emerge relative to effects that index successful retrieval. If emotion and retrieval effects onset together, this would constitute evidence for an effect of emotion on retrieval *per se*. Alternatively, the finding that emotion effects lag behind those of retrieval would be consistent with a 'post-retrieval' locus, that is it would suggest that emotion modulates processes operating on the *products* of retrieval rather than the initial recovery of information from memory.

As discussed in chapter one, a number of characteristic 'old/new' ERP memory effects have been identified in such studies which appear to correlate with different components of retrieval processing (see Friedman and Johnson, 2000; Rugg and Allan, 2000 for reviews). Of these, the most relevant to the present experiment is the 'left-parietal old/new' effect, which onsets around 400ms post-stimulus, has duration of around 500 ms, and is thought be a correlate of episodic retrieval or 'recollection' (Rugg et al, 1996; Smith, 1993; see also chapter 1). A second relevant effect is the 'right frontal old/new effect', which has been proposed as a neural correlate of post-retrieval monitoring (Rugg et al, 1998; Wilding and Rugg, 1996; see also chapter 1).

The present experiment was motivated by the previous ERP findings of Maratos and Rugg (2001), discussed in more detail in chapter 2. In two experiments they investigated the neural correlates of recognition of words encoded in negatively or neutrally valenced sentences. In experiment 1 the test task was old/new recognition.

Words encoded in negative sentences elicited larger 'left parietal' ERP effects than those encoded in neutral sentences and, in addition, elicited a prominent right frontal effect. Since the effects of emotion in this experiment took the form of modulations of old/new effects common to emotional and non-emotional material, Maratos and Rugg (2001) concluded that the findings provided no evidence to suggest that the retrieval of emotional and non-emotional information engaged distinct neural systems.

In their second experiment, Maratos and Rugg (2001) required subjects to make both recognition and source judgements, explicitly discriminating between words which had been encoded in negative vs. neutral sentences. In contrast to the findings of their first experiment, there were now no effects of emotion on either left parietal or right frontal effects, which were large and robust for all correctly recognised words. In light of these findings, Maratos and Rugg (2001) interpreted the results of their first experiment as evidence that contextual information is more likely to be retrieved incidentally, and to capture attention, when it is emotionally valenced.

The first experiment described here investigated the neural correlates of recognised pictures encoded in positively, neutrally or negatively valenced contexts. Pictorial stimuli are likely to be more effective at engaging emotional processing than verbal stimuli because of their highly concrete nature and 'cognitive immediacy'. The use of pictures to provide emotionally valenced contexts may, therefore, lend greater power to the identification of emotion effects on retrieval processing than was afforded by the verbal stimuli employed by Maratos and Rugg (2001). Furthermore, the employment of positive as well as negative contexts allows a distinction to be drawn between valence-specific and valence-independent emotion effects, unlike in the study of Maratos and Rugg.

Methods

Subjects

Twenty four right handed young adults (age range 18-32 years, mean 24.5) were employed as subjects and remunerated at the rate of £7.50/hour. All reported themselves to be in good health with no history of neurological or psychiatric illness. Six subjects were excluded from the final analysis, 2 due to inadequate behavioural performance and 4 due to insufficient trials in critical conditions. Of the 18 subjects contributing data, 6 were female.

Stimulus Materials

Stimuli consisted of two picture components, an object superimposed on a background context. Objects were presented within a yellow box to clearly demarcate their separation from the background. Backgrounds were drawn principally from the International affective pictorial system (IAPS) (Lang et al, 1997), a series of pictures with standardised ratings for valence and arousal. About 5% of the background materials consisted of photographs additional to the IAPS set. 180 backgrounds and 360 object pictures were selected on the basis of pilot studies, as described in chapter 3b.

List Construction

At study, subjects studied one of six study lists. Each list included the 180 selected backgrounds, arranged pseudorandomly, with no more than three pictures from the

same valence category presented consecutively. Each critical object was paired with a neutral background in one list, a negative background in another, a positive background in a third, and was available as a new item for the remaining three lists. The study phase was separated into three parts to allow rest breaks, and the first two background/object pairs in each part were neutral filler items. Therefore each study list consisted of 186 background/object pairs (including the fillers). Each study list had three related test lists, consisting of 180 old items, 90 new items and 6 fillers. Each test list utilised a different set of new items, and each subject would be tested on one of the three test lists. A practice study list of 6 background/object pairs and a practice test list of 9 objects were also constructed and were used to train subjects prior to the experiment proper.

Study Procedure

In the study phase, stimuli were presented in the centre of a colour computer monitor. The background was initially presented alone on the screen for 3s. During this time subjects made a verbal rating of the background's emotional valence using a 5 point Likert scale, ranging from –2 (very unpleasant) to +2 (very pleasant).

3s after presentation of the context, the critical object was superimposed centrally upon the background (see fig 4.1), and subjects were required to imagine a connection between background and object. The connection was made covertly. The object and background were presented together for 5s, and the screen was then blanked for 750ms before presentation of the next background. Six practice trials were given prior to the study proper, during which the subjects were required to describe verbally the connections they had made between background and object, thereby ensuring they

understood the task. During the study phase proper, rest breaks were given after every 62 trials, the first two trials of each of the subphases being fillers.

ERP Recording and Analysis

EEG was recorded from 31 Ag/AgCl electrodes. Twenty-nine of these were embedded in an elasticated cap (Falk Minow Services 'Easycap', http://www.easycap.de/easycap; Montage depicted in Fig. 4.1) and one was attached to each mastoid process. Recordings were made with reference to Fz and subsequently re-referenced to linked mastoids. Vertical and horizontal EOG were recorded from electrode pairs above and below the right eye and on the lateral canthi. EEG and EOG were amplified with a bandwidth of 0.03-30Hz (3 dB points) and digitised (12 bit) at a rate of 125Hz.

The recording epochs began 104ms prior to stimulus onset and had a duration of 2048ms. A correction procedure was used to minimise the number of trials rejected due to blink artefacts, described in chapter 3b, and similar to methods employed previously (e.g Rugg et al, 1997). Trials containing non-blink vertical eye movements or horizontal eye movements were rejected. Trials where A/D saturation occurred or baseline drift exceeded ±40μV were also rejected.

ERPs were formed for correctly rejected new items and correctly recognised old items associated with each valence category (positive, negative and neutral). Waveforms were digitally smoothed with a zero-phase shift low pass filter (3dB down at 19.4Hz). Subjects were excluded if the number of trials contributing to any ERP waveform of experimental interest fell below 16 trials.

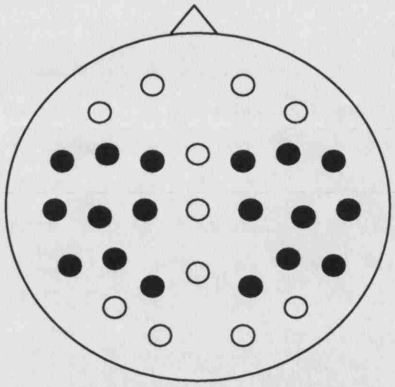

Figure 4.1 Scalp sites used for ERP recording. Black infills depict the sites on which primary analyses were carried out (see results).

Test Procedure

The test phase followed the study phase after a delay of around five minutes, during which a serial subtraction task was used to prevent rehearsal. A white asterisk was presented against a black background for 500ms, following which the stimulus was presented for 750ms; a white fixation cross on a black background was presented for 1750ms before presentation of an asterisk denoted the imminent onset of a new trial, giving a stimulus onset asynchrony of 3s.

Subjects viewed the stimuli whilst resting each forefinger on a microswitch. They were instructed to respond with one finger when the object depicted had been presented in the preceding study phase, and with the other finger if it was being viewed for the first time. Assignment of responses to fingers was counterbalanced across subjects. Instructions were to respond as quickly as possible without sacrificing accuracy. Rest breaks were given after every 92 stimuli, with the first two stimuli of each subphase being filler items. Prior to the test phase proper an example test phase was given, containing the 6 items from the study example, plus 3 new items. None of these items appeared in the subsequent test list.

Results – Experiment 1

Behavioural Data

Mean valence ratings (SD in parentheses) for each class of background were neutral: 0.091 (0.46); positive: 1.21 (0.61); negative: -1.45 (0.64). Ratings for both positive and negative backgrounds differed significantly from neutral background ratings (both $F>100$, $p< 0.001$). The difference in mean ratings between negative and neutral backgrounds was greater than that between positive and neutral backgrounds [$F(1,17) = 44.5$, $p<0.001$].

Mean accuracy and reaction time (RT) for the recognition test are shown in table 4.1. One-way ANOVA of hit rates showed a main effect of condition [$F(1.6,26.7) = 3.85$, $p < 0.05$; (here and in all subsequent ANOVAs, degrees of freedom are adjusted with the Greenhouse-Geisser correction for non-sphericity)]. Planned t-tests were employed to test the prediction that hit rates for items paired with negatively ('negative hits') and positively ('positive hits') valenced backgrounds would exceed the rate for those paired with neutral backgrounds ('neutral hits'). These tests revealed a reliable difference between positive and neutral ($t_{17} = 3.64$, $p < 0.05$), but not between negative and neutral hit rates ($p > 0.5$). A Tukey HSD test revealed that the difference between positive and negative hit rates was marginally significant ($p<.06$).

	Neutral	Negative	Positive	New
Recognition Accuracy	0.80 (0.09)	0.81 (0.09)	0.85 (0.09)	0.92 (0.05)
RT (msec)	964 (312)	977 (399)	953 (277)	1069 (293)

Table 4.1 Mean accuracies and reaction times for experiment 1 (standard deviations in parentheses)

ANOVA of hit RTs revealed no significant effects.

ERP Data

The mean number of trials (range in parentheses) contributing to the average ERPs for each response type were – correct rejections, 41 (20 – 82), neutral hits, 23 (16 – 57), negative hits, 24 (16 – 51), positive hits, 23 (16 – 41). For the reasons given below, the waveforms for the negative and positive hits were collapsed to form a single 'emotional hit' condition. The grand average waveforms for selected electrode sites are shown in figure 4.2. As is evident from figure 4.2, ERPs diverge as a function of condition from around 300ms post stimulus. Old items, encoded in either emotional or neutral backgrounds, elicited more positive going waveforms than did new items, which demonstrated an asymmetry in favour of the left hemisphere over the posterior scalp. This old/new effect persisted until around 1100ms in the ERPs to neutral hits. From around 700ms the ERPs for emotional hits appear to contain an additional positive-going effect. This is most marked at mid-lateral sites, where it persists until the end of the recording epoch.

ERPs were quantified by measuring the mean amplitude of 5 consecutive latency regions (300-500, 500-800, 800-1100, 1100-1400, 1400-1900 msec). These regions were selected on the basis of the timing of memory effects in previous studies (e.g. Maratos and Rugg, 2001; see also Rugg and Allan, 2000) and visual inspection of the present data. Analyses of the ERP data proceeded in several stages. Preliminary analyses demonstrated that the ERPs elicited by the two classes of emotional hit did not differ reliably in any latency range (min $p > .1$); thus the data for these two item types were collapsed prior to the analyses presented below.

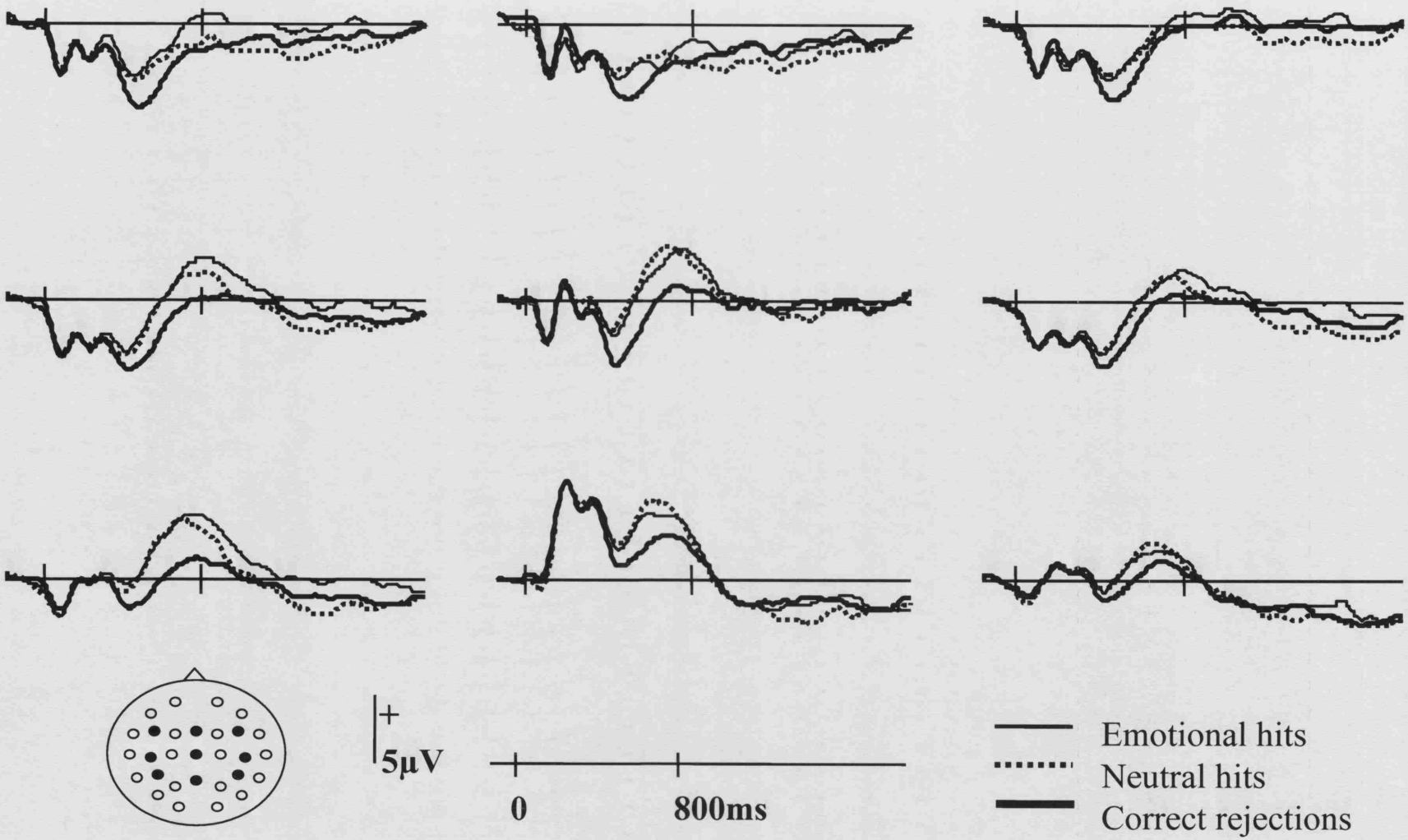

Figure 4.2 Grand average ERP waveforms elicited by correctly classified items in experiment 1. Negative and positive hits have been collapsed into a single set of waveforms. Sites as depicted on the insert.

To assess the effects of item type on ERP amplitude for each latency region, ANOVAs were performed on the data obtained from the electrode sites indicated in figure 4.1. These ANOVAs were factored according to item type (correct rejection, neutral and emotional), hemisphere, antero-posterior (AP) position (frontal, central/temporal, parietal), and lateral site (inferior, middle, superior). For any ANOVA that demonstrated a significant effect involving item type (effects that excluded item type are not reported in either these or follow-up ANOVAs), three subsidiary analyses were conducted to contrast separately neutral hits vs. correct rejections (neutral old/new effects), emotional hits vs. correct rejections (emotional old/new effects) and emotional vs. neutral hits (emotion effects).

A second set of analyses contrasted the scalp topographies of the aforementioned ERP effects. To assess whether the topography of the neutral and emotional old/new effects differed, these were contrasted within all the latency regions in which the effects were independently significant, using the data from all 29 electrode sites. This ANOVA was conducted on difference scores (hit – correct rejection), after normalization with respect to range to obviate the confounding effects of global amplitude differences (McCarthy and Wood, 1985; see chapter 3a). Factors were item type (neutral vs. emotional), latency region, and electrode site. A separate analysis, conducted along similar lines, contrasted the topography of the emotion effects within each of the regions in which they were significant.

Mean Amplitude Analyses

The outcomes of the overall ANOVAs are shown in table 4.2 for each latency region. It can be seen that in each case, reliable effects involving the factor of item type were

Latency Region	300 - 500ms	500 – 800ms	800 - 1100ms	1100 - 1400ms	1400 – 1900ms
All Hits vs. CR					
Item type (IT)	F(1.8,31.2) = 5.57	F(1.7,28.3) = 19.91	F(1.7,29.3) = 12.68	F(1.6,27.8) = 14.29	F(1.5,25) = 15.57
	p < 0.05	p < 0.001	p < 0.001	p < 0.001	p < 0.001
IT x HM	-	F(1.5,26.2) = 7.33	F(1.9,32) = 3.70	-	-
		p = 0.005	p < 0.05		
IT x AP	-	-	F(2.4,41.5) = 4.65	-	-
			p < 0.05		
Neutral hit vs. CR					
Item type (IT)	F(1,17) = 7.13	F(1,17) = 19.88	F(1,17) = 4.78	-	-
	p < 0.05	p < 0.001	p < 0.05		
IT x HM		F(1,17) = 10.35	-	-	-
		p = 0.005			
Emotional hit vs. CR					

Item type (IT)	F(1,17) = 10.21	F(1,17) = 22.00	F(1,17) = 22.19	F(1,17) = 9.42	F(1,17) = 12.1
	p < 0.01	p < 0.001	p < 0.001	P < 0.01	p < 0.005
IT x HM	-	F(1,17) = 13.54	F(1,17) = 8.06	-	-
		p < 0.005	p < 0.05		
Emotional vs. neutral hits					
Item type (IT)	-	-	F(1,17) = 11.08	F(1,17) = 2.09	F(1,17) = 22.02
			p < 0.005	p < 0.001	p < 0.001
IT x HM	-	-	F(1,17) = 4.475	F(1,17) = 4.483	-
			p = 0.05	p = 0.05	
IT x HM x AP x ST	F(2.9,49.4) = 3.041	-	-	-	-
	p < 0.05				

Table 4.2 F-values, degrees of freedom and probabilities associated with main effects and interactions for the 5 examined latency regions in experiment 1. Abbreviations – IT = item type, HM = hemisphere, AP = anteroposterior position.

present. Also shown in the table are the results of the subsidiary ANOVAs for each latency range. The findings are elucidated below, with discussion of neutral old new/effects, emotional old/new effects and emotion effects respectively.

Neutral old/new effects

As shown in table 4.2, a main effect of item type was found for the first three latency regions, reflecting in each case the greater positivity of ERPs to neutral hits. In the 500-800 ms region - when these old/new effects were at their maximum - item type interacted with hemisphere, reflecting the greater size of the old/new effects over the left hemisphere.

Emotional old/new effects

Emotional old/new effects were reliable in every latency region analysed (table 4.2), reflecting greater positivity for emotional hits. The interaction of these effects with hemisphere in the 500-800 and 800-1100 ms regions reflected the left sided preponderance of effects in this part of the epoch.

Effects of Emotion

Table 4.2 also shows the outcomes of the contrasts between emotional and neutral hits. The first difference between the two classes of ERP emerged in the 300-500ms latency range, in the form of a reliable interaction between item type, hemisphere, AP position and lateral site. This interaction reflected a small positive shift in waveforms elicited in the emotional condition, clearest over right lateral posterior temporal scalp.

Greater differences in amplitude emerge from 800ms, after which the waveforms continue to differ until the end of the recording epoch. These differences were larger over the left than the right hemisphere in the 800-1100 ms and 1100-1400 ms latency regions, as evidenced by reliable interactions between item type and hemisphere. In the earlier of these regions, an interaction with the factor of anterior-posterior location indicated the emotion effects were greater over anterior scalp regions.

Topographic Analyses

The ANOVA contrasting the scalp distributions of the neutral and emotional old/new effects was conducted on data from the earliest three latency regions, when the effects were reliable for both effect types. A subset of these distributions is illustrated in figure 4.3. The ANOVA revealed an interaction between latency region, effect type and site [$F(7,118.4) = 2.88$, $p < 0.01$], indicating that the scalp topographies of the two old/new effects changed differentially with time. Subsidiary ANOVAs, conducted on the data from each latency region separately, indicated that the topographies of the effects were did not differ reliably in the earliest two regions, but did do so in the 800-1100 ms region [$F(4.6,78.6) = 3.06$, $p<0.05$].

The scalp topographies of the emotion effects (i.e. the differences between emotional and neutral hits) are illustrated in figure 4.4 for the three latency regions in which they were reliable (800-1100, 1100-1400 and 1400-1900ms). ANOVA revealed a significant latency region by site interaction [$F(5.2,88.5) = 2.72$, $p<0.05$] reflecting the transition from a distribution that is initially maximal over the frontal and left temporal scalp to one more diffusely distributed over the lateral scalp.

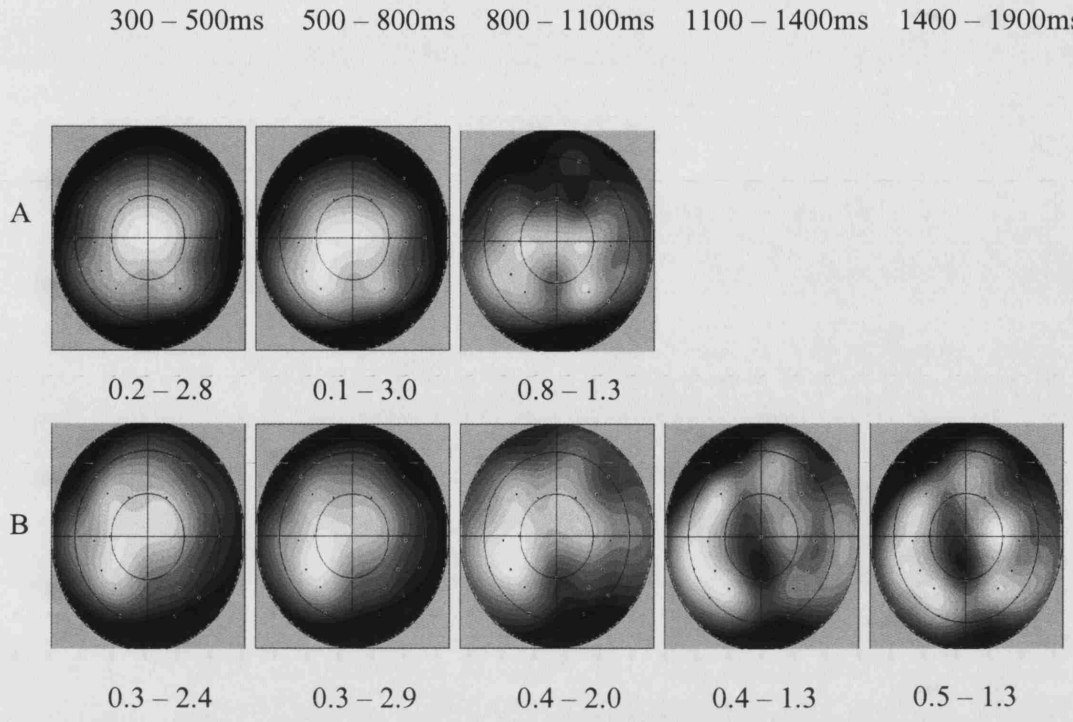

Figure 4.3 Spherical spline maps showing scalp distributions of the old new/effects associated with recognition of items encoded in neutrally (A) and emotionally (B) valenced contexts in the latency regions (from left to right) 300-800ms, 800-1100ms, 1100-1900ms poststimulus. Each map is proportionately scaled between the extremes of the depicted effect (values in μV given below in each case).

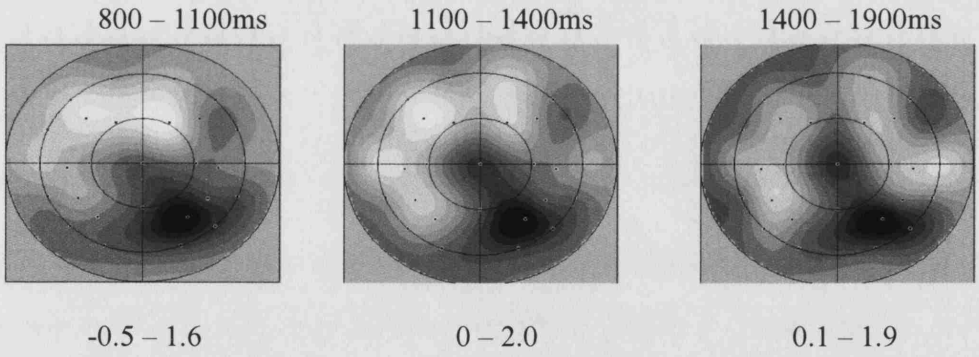

Figure 4.4 Spherical spline maps showing the scalp distributions of the emotion effect from experiment 1 in the latency regions shown. Each map is proportionately scaled between the extremes of the depicted effect (values in μV given below in each case).

Discussion

Behavioural Data

Items associated with positive contexts were recognised at a slightly, but significantly, higher level of accuracy than items encoded in either neutral or negative contexts. This result supports previous findings indicating that emotion can modulate recognition memory (e.g. Tabert et al, 2001), but suggests that such effects are subtle. The difference in recognition accuracy between items associated with positive and negative valences was not predicted, and is not easily explained in terms of the arousal or absolute valence associated with the positive and negative backgrounds. One possibility is that subjects were more likely to fail to encode objects associated with negative contexts because of the extreme, 'attention-grabbing' nature of some of the scenes forming these contexts. By this argument, when contexts are particularly arousing they may automatically capture a considerable amount of attention. Attentional resources are limited, and it may be that excessive capture by strongly arousing contexts detracts from the amount of attention which can be dedicated to encoding of the associated objects. Division of attention during encoding has been shown to impair subsequent recognition performance (e.g. Craik et al 1996; see also chapter 1) and may explain the results obtained here, although the difference between positive and negative hits was only marginally significant, so this interpretation is only tentative.

ERP Data

In line with many earlier reports (see Rugg and Allan, 2000), correctly recognised items elicited ERPs that were more positive than those elicited by correctly rejected

new items. This difference was evident from around 300ms post-stimulus and, from around 500 ms, displayed the posterior asymmetry characteristic of the left parietal old/new effect (see Introduction). In contrast to a previous study (Maratos and Rugg, 2001) this effect was not enhanced for recognised items which had been encoded in emotional as opposed to neutral contexts. On the assumption that the left parietal effect is a neural correlate of episodic retrieval ('recollection'; for reviews see Rugg and Allan, 2000; Friedman and Johnson, 2000; see also chapter 1), this finding suggests that, unlike in the experiment of Maratos and Rugg, emotion influenced neither the probability of successful recollection, nor the amount of episodic information that was retrieved. In the present experiment, the most evident ERP effects of emotion emerged around 800ms post-stimulus, some 500ms after the onset of the aforementioned old/new effects. The relatively late onset of these emotion effects suggests that they reflect an emotional modulation of 'post-retrieval' processing, rather than processes directly reflecting retrieval *per se* (see introduction). In addition, an effect of emotion was present early in the recording epoch, onsetting around 300ms post-stimulus. This effect was, however, small in amplitude and subsidiary analyses of data from the electrode sites where the effect was greatest gave rise only to weakly significant effects. Further discussion of these early effects is deferred until chapter 6, when data from this early latency region is analysed across multiple experiments.

The present emotional old/new effects had scalp distributions supporting the presence of activity additional to that reflected by neutral old/new effects. This finding suggests that additional neural populations, and hence cognitive processes, were engaged by the retrieval of emotional relative to neutral material. The present findings differ from those of Maratos and Rugg's (2001) experiment 1 in three important

respects. First, as already noted, the manipulation of emotional context failed in the present case to influence the amplitude of the left parietal old/new effect. Second, this manipulation modulated the so-called right frontal effect only weakly at best (see Fig 3). Third, the principal effects of emotion were manifest in a pattern of a late ERP modulation which does not appear to resemble previously reported ERP old/new effects, raising the possibility of the engagement of emotion-specific (post-retrieval) processing.

Several other studies utilising pictures from the IAPS set (from which the majority of our contexts were drawn) have reported a 'late positive potential' (LPP) ERP effect which differentiates emotional from neutral pictures during either their active evaluation (e.g. Cacioppo et al, 1996; Schupp et al, 2000), active encoding (e.g. Dolcos and Cabeza, 2003) or passive viewing (e.g. Keil et al, 2002). The amplitude of this effect has been reported to correlate with both arousal ratings and magnitude of galvanic skin response (GSR) (Cuthbert et al, 2000), but not interact with valence (negative vs. positive). It has been proposed that the LPP reflects motivational engagement and commitment of attentional resources to the processing of affective material (Lang et al, 1997; cf. Schupp et al, 2000; Cuthbert et al, 2000). Thus, one explanation for the late-onsetting emotion effect observed in the present experiment is that it reflects the engagement of similar processes, but in response to information retrieved from memory rather than present in the external environment. The onset of the emotion effects in the present experiment (ca. 700 ms) was somewhat later than the onset of the effects reported in the studies cited above (ca. 400ms). Presumably, this is a consequence of the difference in the time required to respond to emotionally valenced information available directly from the environment, as opposed to information available only indirectly in the form of retrieved episodic information.

As in experiment 1 of Maratos and Rugg (2001), the effects of emotion in the present experiment were observed in a yes/no recognition task in which the explicit retrieval and identification of the study context was unnecessary. Thus, the effects of emotion were presumably a consequence of the incidental retrieval and subsequent processing of contextual information. This raises the possibility that these effects reflect the engagement of emotionally non-specific processes that are more easily triggered by task-irrelevant episodic information when it is highly salient than when it is not.

Another general difficulty in interpreting studies of emotion relates to features of emotional stimuli, not directly related to their emotionality, which differ from neutral stimuli (see chapter 2). A key question when considering any cognitive or neural effect attributed to emotion is whether that effect is qualitatively replicable by comparing subsets of neutral stimuli. In particular, emotional stimuli are typically more novel, more interesting (Hamann et al, 1999) and more closely semantically related to one another (Phelps et al, 1997), in addition to their emotional attributes. Whilst this effect is ameliorated somewhat by avoiding the presentation of emotional items at test, nonetheless it is worthwhile investigating whether non-emotional aspects of the contexts may have contributed to the modulation of retrieval activity.

Experiment 2: Effects of Interest and Novelty

In order to address the aforementioned issue about non-emotional differences between contexts, a second control study was carried out where in addition to comparing old/new effects for items encoded in neutral and emotional contexts, an additional set of neutral items of lower novelty and interest than the standard set of neutral items. If differences between emotional and neutral items can be explained (exclusively) in

terms of novelty and/or interest then qualitatively (if not quantitatively) similar differences would be expected between the high and low interest neutral items as between the emotional and high interest neutral items.

In order to separate high and low interest items, 6 subjects rated a large number of our pool of neutral contexts (see chapter 3b) as to how interesting and novel they were. Although it was possible to form two groups of neutral items which were significantly different in their ratings of both these attributes, these differences were relatively small, raising concerns that any between-group effects might be too small to be easily detected. Repetition of items makes them less novel, and may make them less interesting hence we decided to compare old/new effects from objects studied with either emotional backgrounds, high interest neutral backgrounds or neutral backgrounds which were rated as low interest and also repeated several times (each time with unique items) during the study phase. It was predicted that if the emotion effects described in experiment one were due to differences in novelty of or interest in the emotional vs. neutral backgrounds that qualitatively similar differences should be observed between emotional vs. neutral and high vs. low interest neutral conditions.

Methods – Experiment 2

Subjects

Nine right handed young adults (age range 19-28 years, mean 24) were employed as subjects and remunerated at the rate of £7.50/hour. All reported themselves to be in good health with no history of neurological or psychiatric illness. One subject was excluded from the final analysis due to insufficient trials in critical conditions. Of the 8 subjects contributing data, 4 were female.

Stimulus Materials

Stimuli consisted of two picture components, as for experiment 1. The same pool of objects was used as described in chapter 3b. Forty negative and positive pictures with the smallest variance in their valence ratings were selected as positive and negative contexts. Forty 'high interest' (mean 3.1, SD 0.76) and five 'low interest' (mean 1.6, SD 0.43) backgrounds were selected on the basis of pilot studies where 6 subjects rated pictures in terms of their novelty and how interesting they were on 5 point Likert scales. These were used for the high and low interest neutral contexts, with the contexts repeated eight times in the low interest condition.

List Construction

At study, subjects studied one of eight study lists. Each list included the contexts described above, arranged pseudorandomly, with the low interest contexts repeated four times each and no more than three pictures from the same condition presented consecutively. Each critical object was paired with a high interest neutral background in one list, a low interest/repeated background in a second, a negative background in another, a positive background in a fourth, and was available as a new item for the remaining four lists. The study phase was separated into two parts to allow rest breaks, and the first two background/object pairs in each part were neutral filler items. Therefore each study list consisted of 164 background/object pairs (including the fillers). Each study list had three related test lists, consisting of 160 old items, 80 new items and 4 fillers. Each test list utilised a different set of new items, and each subject would be tested on one of the three test lists. A practice study list of 6

background/object pairs and a practice test list of 9 objects were also constructed and were used to train subjects prior to the experiment proper.

Other methods

The methods for study and test phases and ERP recording were essentially identical to those described for experiment 1 and will not be repeated here.

Results

Behavioural Data

Mean valence ratings (SD in parentheses) for each class of background were neutral: 0.198 (0.56); repeated: 0.042 (0.39); positive: 1.21 (0.61); negative: -1.45 (0.64). Ratings for both positive and negative backgrounds differed significantly from ratings of both repeated and unrepeated neutral backgrounds (all $F>100$, $p< 0.001$). The difference in mean ratings between negative and neutral backgrounds was greater than that between positive and neutral [$F(1,17) = 44.5$, $p<0.001$].

Mean accuracy and reaction time (RT) at test are shown in table 4.3. One-way ANOVA of hit rates showed a marginal effect of condition [$F(1.5,10.8) = 3.77$, $p < 0.06$; here and in all subsequent ANOVAs, degrees of freedom are corrected after application of the Greenhouse-Geisser correction for non-sphericity]. Planned t-tests were employed to test for predicted differences between hit rates for items paired with positively valenced backgrounds ('positive hits') would exceed the rate for those paired with other types of hit. Additional tests contrasted negative hits with hits to items presented against repeated and unrepeated neutral backgrounds, and contrasted

	Neutral REP	Neutral HI	Negative	Positive	New
Recognition Accuracy	0.79 (0.08)	0.81 (0.10)	0.78 (0.07)	0.85 (0.09)	0.87 (0.04)
RT (msec)	911 (288)	877 (282)	902 (379)	897 (312)	1103 (299)

Table 4.3 Mean accuracies and reaction times for experiment 2 (standard deviations in parentheses)

neutral and repeat hit rates. The tests revealed reliable differences between positive and neutral hits ($t_7 = 2.91$, $p < 0.05$), positive and repeat hits ($t_7 = 3.30$, $p < 0.05$) and positive and negative hits ($t_7 = 2.40$, $p < 0.05$). No significant differences were found between neutral, repeat and negative hit rates (all $p > 0.2$).

ERP Data

The mean number of trials (range in parentheses) contributing to the average ERPs for each response type were – correct rejections, 43 (22 – 72), neutral high interest hits, 25 (16 – 32), repeated hits, 24 (19 – 31), negative hits, 22 (16 – 28), positive hits, 25 (18 – 32). Figures 4.5 and 4.6 show grand average waveforms for selected electrode sites contrasting unrepeated (high interest) neutral hits, repeated (low interest) neutral hits and correct rejections (fig 4.5) and emotional (collapsed across positive/negative) hits, neutral (collapsed repeated/unrepeated) hits and correct rejections (fig 4.6) respectively.

As is evident from figures 4.5 and 4.6, ERPs diverge as a function of condition from around 300ms post stimulus. All classes of old item elicited a positivity relative to the new items, onsetting earliest at midfrontal sites, where it persisted until around 800ms

post-stimulus, whilst over left parietal sites an old/new effect persisted until around 1000ms post-stimulus in the ERPs to neutral and repeated hits. No differences were apparent in the ERPs to neutral and repeated hits. From around 600ms post-stimulus, the ERPs for both classes of emotional hits contain an additional positive-going effect. This is most marked at left frontal sites, where it persists until the end of the recording epoch.

ERPs were quantified by measuring the mean amplitude of 5 consecutive latency regions, as described for experiment 1. As in that experiment, ANOVAs were performed on the data obtained from the electrode sites indicated in figure 4.2. These ANOVAs were factored according to item type (correct rejection, neutral high interest, neutral low interest positive and negative), hemisphere, antero-posterior (AP) position (frontal, central/temporal, parietal), and lateral site (inferior, middle, superior). For any ANOVA that demonstrated a significant effect involving item type (effects that excluded item type are not reported in either these or follow-up ANOVAs), subsidiary analyses were conducted to contrast separately each class of hit vs. correct rejections (old/new effects), neutral unrepeated hits vs. repeated hits (repetition effects), each class of emotional hits vs. each class of neutral hits (emotion effects) and negative hits vs. positive hits (valence specific effects).

As in experiment 1, a second set of analyses contrasted the scalp topographies within all the latency regions in which the effects were independently significant, using the data from all 29 electrode sites. This ANOVA was conducted on difference scores (hit – correct rejection) after normalization (see chapter 3a).

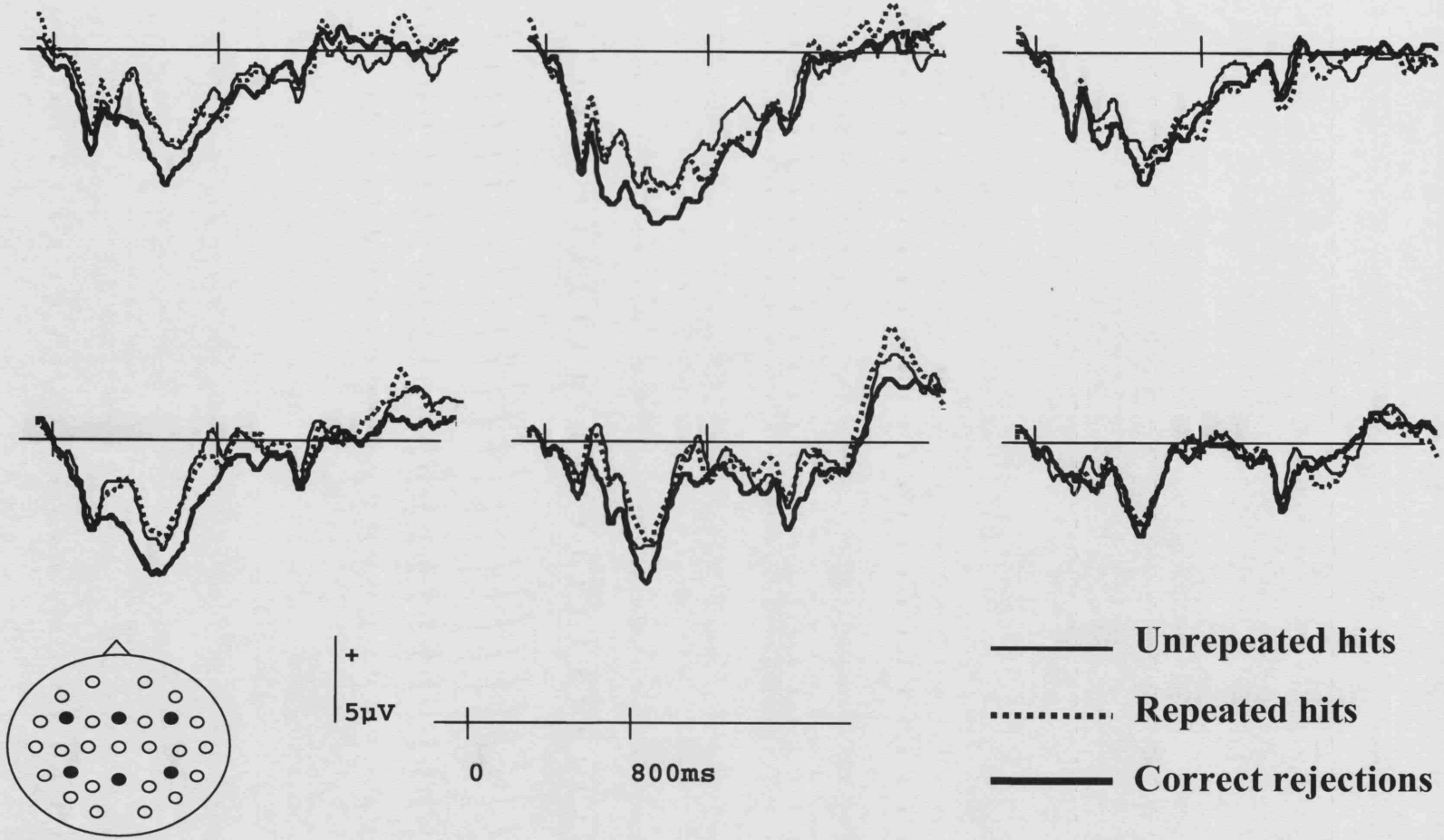

Figure 4.5 Grand average ERP waveforms elicited by correctly classified neutral items in experiment 2. Sites as depicted on the insert.

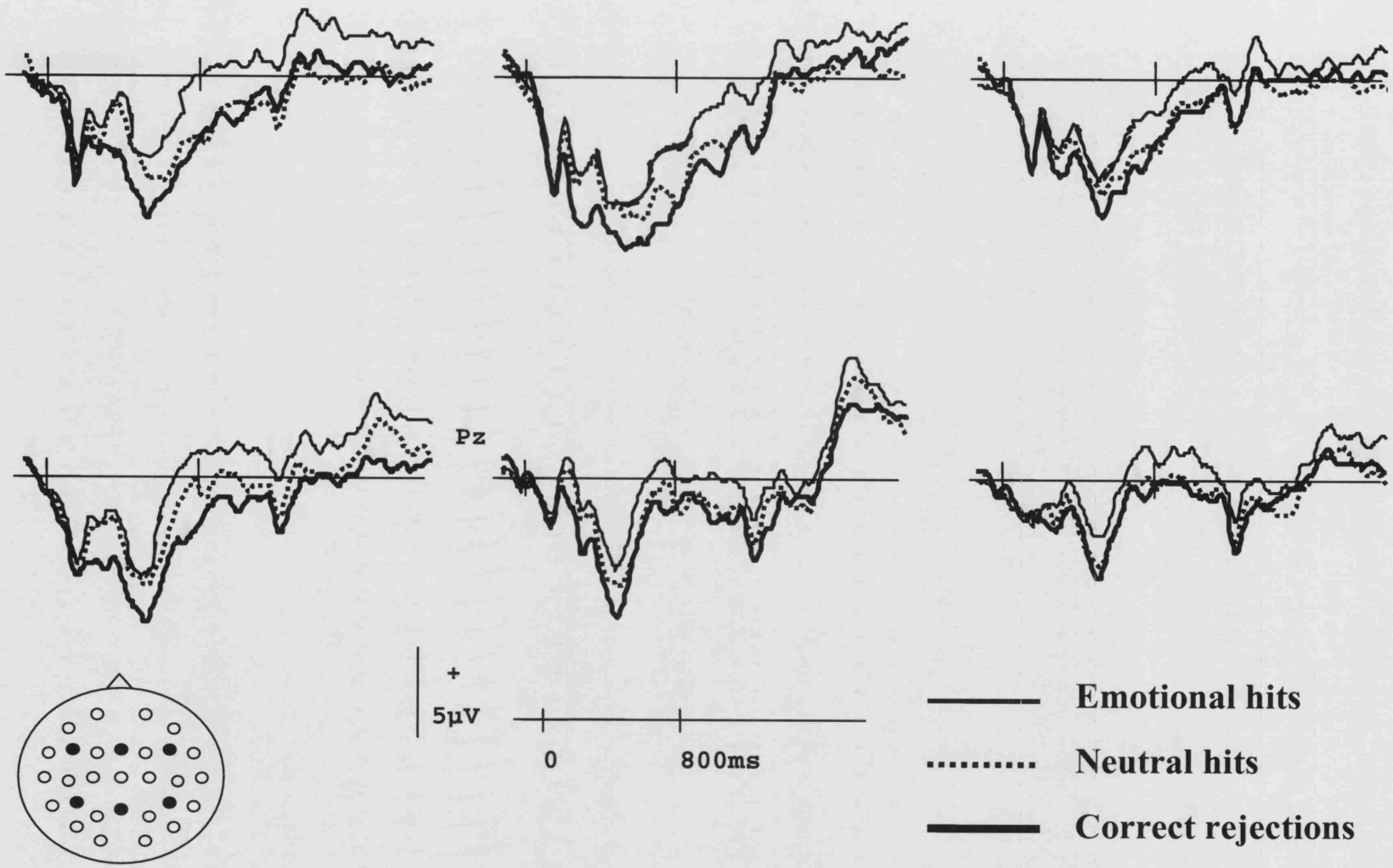

Figure 4.6 Grand average ERP waveforms elicited by correctly classified items in experiment 2. Neutral hits collapsed across repeated and unrepeated trials. Emotional hits collapsed across positive and negative valences. Sites as depicted on the insert.

Mean Amplitude Analyses

The outcomes of the overall ANOVAs are shown in table 4.4 for each latency region. It can be seen that in each case, reliable effects involving the factor of item type were present. Also shown in the table are the results of the subsidiary ANOVAs for each latency range. We elucidate these below, discussing the neutral old new/effects, emotional old/new effects and emotional effects respectively.

Neutral old/new effects

As shown in table 4.4, interactions incorporating item type were found for the first three latency regions, reflecting in each case the greater positivity for ERPs to neutral hits. These were tested for both high and low interest neutral conditions independently. In each case the interactions reflect the reflecting the greater size of old/new effects over the left hemisphere, particularly at posterior sites.

Emotional old/new effects

Emotional old/new effects were reliable in every latency region analysed, reflecting greater positivity for the emotional hits. The interaction of these effects with hemisphere in the 500-800 ms and 800-1100 ms regions reflected the left sided preponderance of the effects in this part of the epoch.

Effects of Emotion

Table 4.4 shows the outcomes of the contrasts between emotional and neutral hits. Differences in amplitude emerged from 800ms, after which waveforms continue to

Latency Region	300 – 500ms	500 – 800ms	800 - 1100ms	1100 - 1400ms	1400 – 1900ms
All Hits vs. CR					
Item type (IT)	F(2.2, 15.7) = 5.41	F (1.8, 12.7) = 18.57	F(2.1, 14.6) = 5.1	F(2.2, 15.4) = 4.19	F(1.9, 13.4) = 4.65
	$p < 0.05$	$p < 0.001$	$p < 0.05$	$p < 0.05$	$p < 0.05$
IT x HM	-	F(2.3, 16.2) = 6.16	-	-	-
		$p < 0.01$			
IT x HM x AP x ST	F(2.4, 17) = 3.79	F(2.7, 19.2) = 5.37	-	-	-
	$p < 0.01$	$p < 0.01$			
Neutral (REP) hit vs. CR					
IT x HM x AP	F(1.3, 9.2) = 9.8	F(1.1, 8) = 5.95	-	-	-
	$p < 0.01$	$p < 0.05$			
Neutral (HI) hit vs. CR					
IT x HM	F(1,7) = 14.1	F(1,7) = 7.1	-	-	-

	$p < 0.01$	$P < 0.05$			
Emotional vs. neutral hits					
Item type (IT)	-	-	$F(1.6, 11.2) = 5.72$	$F(1.9, 13.4) = 14.52$	$F(1.9, 13.4) = 4.65$
			$p < 0.05$	$p < 0.001$	$p < 0.05$
IT x HM	-	-	$F(1.2, 8.7) = 6.9$	$F(2, 13.9) = 8.346$	$F(1.6, 11.4) = 47.1$
			$p < 0.05$	$p < 0.005$	$p < 0.001$
IT x AP x ST	-	-	-	$F(3, 20.9) = 3.1$	-
				$p < 0.05$	

Table 4.4 F-values, degrees of freedom and probabilities associated with main effects and interactions at the lateral electrode sites indicated in figure 4.1 for the 5 examined latency regions in experiment 2. Abbreviations – IT = item type, HM = hemisphere, AP = anteroposterior position.

differ until the end of the recording epoch. These differences were greater over the left than the right hemisphere in each of the epochs 800-1100, 1100-1400 and 1400-1900ms, as evidenced by reliable interactions between item type and hemisphere. In the 1100-1400 ms epoch an interaction of item type, anterior-posterior position and lateral site reflected the more medial distribution of emotion effects over anterior scalp.

Topographic Analyses

The ANOVA contrasting the scalp distributions of the neutral and emotional old/new effects was conducted on data from the earliest three latency regions, when the effects were reliable for both item types. The ANOVA revealed an interaction between latency region, item type and site [$F(7,118.4) = 2.88$, $p < 0.01$], indicating that the scalp topographies of the two old/new effects changed differentially with time. Subsidiary ANOVAs, conducted on the data from each latency region separately, indicated that the topographies of the effects were did not differ reliably in the earliest

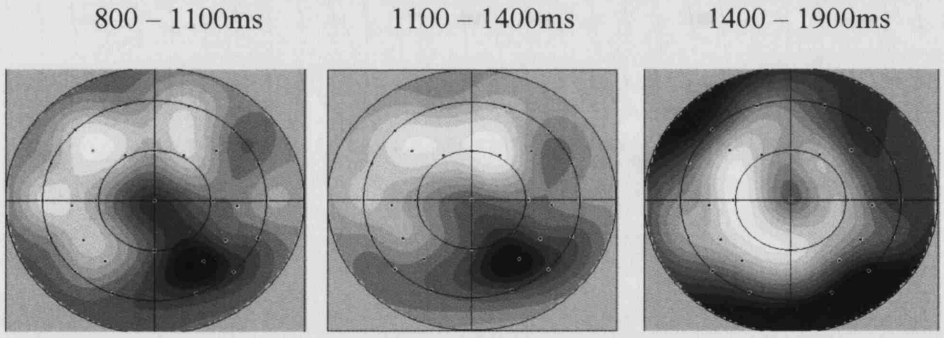

Figure 4.7 Spherical spline maps showing the scalp distributions of the emotion effect from experiment 2 in the latency regions shown. Each map is proportionately scaled between the extremes of the depicted effect (values in μV given below in each case).

two epochs, but did do so in the 800-1100 ms region [$F(2,14) = 4.19$, $p<0.05$]. The scalp topographies of the emotion effects (i.e. the differences between emotional and neutral hits) are illustrated in figure 4.7 for the three latency regions in which they were reliable (800-1100, 1100-1400 and 1400-1900ms). No statistically reliable differences were found over time.

Discussion

The behavioural findings supported the findings from experiment one, in showing a recognition advantage for items encoded in positive contexts. As in experiment 1, significant differences were found between ERPs associated with emotional and neutral hits, onsetting subsequent to the left parietal effect. Importantly, there was no evidence for differences in the ERPs to high and low interest neutral hits. This finding represents evidence against the proposal that the reported emotion effects can be explained in terms of the greater novelty and interest of emotional vs. neutral contexts. Strong conclusions cannot be drawn on the basis of null findings in one condition, but the finding of significant emotion effects together with the absence of any evidence of effects related to context novelty implies that such effects are unlikely to account fully for the observed effects of emotional context.

Summary

This chapter has described two experiments investigating the effects on recognition memory of encoding object pictures in emotional and neutral contexts. Evidence was found for an improvement of recognition performance for items encoded in positive compared to both neutral and negative contexts. This suggests that association of

items with emotional contexts, at least if they are positive, can enhance the probability of their later recognition, in line with previous findings of enhanced memory for emotional items (see introduction; chapter 2).

Furthermore we identified late-onsetting emotion related differences in ERP waveforms to correct recognition of items encoded in emotional vs. neutral backgrounds. We found no evidence to suggest that these effects could be explained in terms of how novel or interesting the emotional contexts were relative to their neutral counterparts. These emotion effects onset subsequent to the left parietal effect, suggesting that they might reflect specific processing on the products of emotional memory retrieval. There was also some evidence for a change of the scalp topography of these effects over time, suggesting that at least two additional and distinct processes may operate on the products of emotional vs. neutral retrieval. Furthermore, there was some evidence for a small emotion-related modulation prior to the onset of the left parietal effect, suggesting that some effects of emotion may act prior to or on retrieval processes *per se*.

It is however unclear as to whether these effects reflect processes which specifically operate during retrieval of emotional memories, or whether they reflect processes which are automatically engaged by emotional memories, but can also be engaged by neutral memories if they are task relevant. This issue, together with the dependency or otherwise of these effects on successful retrieval of emotional information, is addressed in chapter 6.

Chapter 5: fMRI Correlates of the Incidental Retrieval of Emotional Context

Introduction

In the previous chapter, ERP evidence was presented for distinct neural processes supporting the retrieval of emotional and neutral memories. This chapter details an experiment which used fMRI to examine haemodynamic changes associated with retrieval of these different types of memory. A few previous studies have examined interactions between emotion and memory at the time of retrieval, and identified differences in neural activity associated with retrieval of emotional vs. neutral information. Both Taylor et al (1998) and Dolan et al (2000) examined differences in neural activity elicited during recognition of emotional vs. neutral pictures. Taylor et al (1998) reported that recognition of emotional pictures enhanced activity in visual areas, whilst Dolan and colleagues (2000) reported effects in anterior temporal lobe and amygdala during emotional retrieval (see chapter 2 for more details of these studies). Both studies, however, utilised blocked designs, making it difficult to unequivocally separate state- and item-related effects (see Otten et al, 2002; see also chapter 3a). Furthermore, the reliance upon emotional and neutral pictures as recognition cues leads to difficulties in interpreting whether the observed effects reflected exclusively memory-related processes or included activity resulting from on-line processing of emotional information (see chapter 2).

One fMRI study employing an event-related design, has investigated emotional retrieval with a design enabling contrasts of neural activity elicited by recognition of pre-experimental neutral items according to the valence of the study context (Maratos

et al, 2001). They examined activity elicited during a recognition memory test for words presented at study in the context of negative, neutral or positive sentences (Maratos et al, 2001), analogous to the design employed in the ERP experiments described in the previous chapter. Recognition of items encoded in negative vs. neutral sentences elicited increased neural activity in right prefrontal cortex and bilateral medial, superior and anterior temporal regions, including left hippocampus and amygdala. These findings are suggestive of enhanced memory processing and additional emotion-specific processing for these items arising from their study history. Words encoded in positive sentences showed increased activity in bilateral orbitofrontal and inferior frontal areas, left anterior and superior temporal lobes, with trends towards effects in the same regions of amygdala and hippocampus as revealed in the negative vs. neutral contrast. As discussed in chapter 2, a number of these areas have been identified as playing important roles both in emotional processing generally, and specifically in emotional memory.

The present chapter describes an event-related fMRI experiment similar to the first ERP experiment described in chapter 4. The aim was to identify neural structures and circuits supporting successful recognition of items associated at study with emotionally valenced as opposed to neutrally valenced visual contexts. As in the experiments described in the previous chapter, the experimental design employed allowed us to determine which effects reflected qualitative differences in the retrieval of emotional and non-emotional memories, and which reflected enhanced activity in areas also engaged during retrieval of neutral memories. Furthermore, the design enabled assessment of which emotion effects were common to recognition of items encoded in negative and positive memories, and which reflected effects specific to one valence or the other.

Based on the ERP findings described previously, and the fMRI study of Maratos et al (2001), it was anticipated that structures involved in emotional retrieval would include those implicated in the processing of emotional stimuli and events, notably the amygdala and orbitofrontal cortices (see Dolan, 2002; Zald, 2003; Bechara et al, 2000 for reviews), together with enhanced activity in areas more generally associated with memory retrieval, such as parahippocampal cortex, hippocampus and prefrontal cortex. The ERP findings also suggested that the majority of emotion effects would be valence-independent, that is equivalent for items from positive and negative contexts, and that effects would be predominantly left lateralised. However, given the different sensitivities of fMRI and ERPs (see chapter 3a), these hypotheses are only tentative.

One additional question of interest was whether emotion effects elicited during retrieval overlapped with emotion-related differences observed during encoding. One view of memory storage is that elements of memory traces are stored within the sensory specific cortices active during encoding, with the hippocampus binding these representations into a coherent whole (Marr, 1971). Evidence for overlapping activity at encoding and retrieval has been found in previous studies (e.g. Nyberg et al, 2000; Wheeler et al, 2000; Gottfried et al, 2004; see chapter 2). Along similar lines, it might be that the affective components of experiences are stored in emotion-sensitive structures, with the prediction that differences in activity common to encoding and retrieval of emotional vs. neutral memories might reflect the recapitulation of the processes elicited by initial exposure to emotional material.

Methods

Subjects

Eighteen right handed young adults (age range 18-32 years, mean 23) were employed as subjects and remunerated at £7.50/hour. All were in good health with no history of neurological or psychiatric illness. Three subjects were excluded from the final analysis, one due to inadequate behavioural performance, one due to excessive movement artifact, and one due to technical problems. Of the remaining 15 subjects, 8 were female. The experiment conformed to a type approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Stimulus Materials and List Construction

Stimuli consisted of two picture components, an object superimposed on a background context. The stimuli employed were those used in experiment 1 of the previous chapter, and described in chapter 3b, and these details will not be repeated here.

Study Procedure

In the study phase, stimuli were presented via a mirror mounted on the head coil of the fMRI scanner, in direct view of the supine participant, at a distance of approximately 50cm from the projection screen. The background was initially presented alone on the screen for 3s. During this time subjects indicated whether they judged the backgrounds to be pleasant, unpleasant or neutral, using a keypad in the right hand to assign them to these 3 categories. 3s after presentation of the context, the critical object was superimposed centrally upon the background, and subjects were required to imagine a connection between background and object. This connection

was made covertly. The object and background were presented together for 4.5s, and the screen was then blanked for 750ms before presentation of the next background. Six practice trials were given prior to the study proper, during which the subjects were required to describe verbally the connections they had made between background and object, thereby ensuring they understood the task. During the study phase proper, a rest break was given after 92 trials, the first two trials of each of the subphases being neutral filler items.

Test Procedure

The test phase followed the study phase after a delay of around five minutes, during which a serial subtraction task was performed to prevent rehearsal. Stimulus delivery used the same setup as during study. A white asterisk was presented against a black background for 500ms, following which the test item was presented for a period of 750ms. This was followed by a white fixation cross on a black background for approximately 2s before presentation of the asterisk denoted the imminent onset of a new trial. This sequence of events gave a stimulus onset asynchrony (SOA) of 3.25s. 120 'null events', consisting of the white fixation cross for an additional 1.25s in place of the white asterisk and test item, were incorporated into the test list, allowing estimation of baseline. Subjects were instructed to respond, as quickly and accurately as possible, with one button of the keypad when the object depicted had been presented in the preceding study phase, and with another button if it was being viewed for the first time. Assignment of finger responses was counterbalanced across subjects. The test list was split into 2 equal parts, with the first two stimuli of each subphase being filler items. Prior to the test phase proper an example test phase was

given, containing the 6 items from the practice study list, plus 3 new items. None of these items appeared in the subsequent test list.

Imaging and Image Processing

MRI data were acquired from a 1.5T Siemens SONATA system (Siemens, Erlangen, Germany) equipped with a head coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD (blood oxygenation level dependent) contrast, with a repetition time (TR) = 2.7s, giving an effective sampling rate of approximately 2Hz at both study and test. 30 slices of 2.5mm thickness were acquired, with an inter-slice gap of 1.3mm, giving whole brain coverage, with the exception of the vertex. Data were acquired during four separate sessions (two each at study and test) with the first five volumes of each session discarded to allow for T1 equilibration effects. Images were realigned, slice-time corrected, normalised to a standard echo-planar image template and smoothed with a Gaussian kernel with full-width half maximum of 8mm.

Statistical Analysis of Images

Data were analysed using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, UK; Friston et al, 1995) using a random-effects analysis. Test data were modeled as 8 discrete event types: old items from each of the 3 categories of old items (neutral, negative, positive) were separated according to whether they were correctly judged as old (hits) or incorrectly judged to be new (misses), new items were separated into those which were correctly rejected as new (correct rejections), or incorrectly judged to be old (false alarms). Also modeled

separately were the two filler items at the start of each list, and those trials where no response was logged. Principal contrasts were between those events which received correct responses (i.e. hits and correct rejections).

Study data were modeled as 9s epochs of 7 types. Each class of encoding event was divided into those items which were recognised in the subsequent test phase and those which were not, with a final event type consisting of the filler trials at the start of each study list and events where responses were not logged. Analyses were restricted to those items which were subsequently correctly recognised, so as to ensure that contrasts revealed emotion effects, rather than 'subsequent memory effects', which could arise if different proportions of forgotten and remembered items were obtained in the different valence categories.

Regressors modeling events and epochs were convolved with a standard canonical haemodynamic response function, along with its temporal and dispersion derivatives (Friston et al, 1998a). For the analyses of both study and test data, movement parameters were modeled as potentially confounding covariates. For both study and test, assignment of stimuli to valence categories was based on the judgments of each individual subject. Linear contrasts of parameter estimates were estimated for each subject, and initial statistical parametric maps (SPMs) were generated on the basis of an ANOVA incorporating the canonical HRF and its derivatives (see above) for each condition (corrected for non-sphericity using a restricted maximum likelihood (ReML) procedure; Friston et al (2002)). All significant effects obtained with this contrast were found to be carried by the canonical HRF, so subsequent analyses were based on SPMs of the t-statistic derived from contrasts utilizing this basis function alone. For some contrasts, positive and negative hits were collapsed to form a single 'emotional hit' condition, analogous to the previously described ERP studies.

Results

Behavioural Results

Recognition accuracies, and associated reaction times (RTs), are shown in table 5.1. ANOVA conducted on hit rates showed a main effect of condition on recognition accuracy [$F(1.4, 20) = 7.65$; $p < 0.01$]. Subsidiary ANOVAs revealed that items encoded in positively valenced contexts were more likely to be recognised than items encoded in neutrally [$F(1,14) = 38.6$; $p < 0.001$] or negatively [$F(1,14) = 5.87$; $p < 0.05$] valenced contexts. There was no significant difference in the recognition rates for items encoded in negatively versus neutrally valenced contexts ($F < 1$). There were no significant differences in RTs to hits.

fMRI data

The principal contrasts of interest were i) common effects for the three hit conditions (neutral, negative and positive) vs. correct rejections (old/new effects), ii) between a collapsed emotional hit condition (weighted combination of positive and negative hits) and neutral hits (valence-independent emotion effects) and iii) between positive

Table 5.1 Mean accuracies and reaction times (standard deviations in parentheses)

	Neutral	Negative	Positive	New
Accuracy	0.79 (0.09)	0.80 (0.09)	0.84 (0.08)	0.90 (0.07)
RT (msec)	958 (224)	948 (212)	945 (250)	1036 (260)

and negative hits (valence-specific effects). The mean number of trials (range in parentheses) contributing to each of the critical conditions were: neutral hits, 44 (33-55); negative hits, 45 (30-59); positive hits, 46 (30-58); correct rejections, 75 (50-87). The reported contrasts were all based on one-tailed t-tests with a significance level of $p<0.001$, and a spatial extent threshold of at least 5 contiguous voxels. In a number of cases contrasts were used as 'masks' for one another. 'Inclusive' masking reveals voxels common to two or more contrasts, allowing characterisation of brain areas sensitive to a common feature of different contrasts (such as old vs. new for different item categories), as well as areas sensitive to multiple experimental factors (such as memory and emotion). 'Exclusive' masks reveal voxels in one contrast that do not overlap with those from one or more different contrasts, implying specificity of the effects elicited.

Unless stated otherwise, 'inclusive' masks employed contrasts thresholded at $p<0.001$, whilst 'exclusive' masks were thresholded at $p<0.05$ (the lower significance level here increases the confidence with which it can be concluded that 2 contrasts did not overlap).

Common Old/new effects

An *inclusive* mask incorporating old/new effects (i.e. hit-correct rejection contrasts) from neutral, negative and positive hits revealed memory effects common to retrieval of emotional and neutral memories (table 5.2). Significant effects were elicited in left lateral parietal and posterior cingulate cortex, precuneus, angular gyrus, middle temporal gyrus, and left prefrontal cortex (fig. 5.1). These areas correspond closely to those reported in other event-related fMRI studies of recognition memory (e.g.

Henson et al, 1999a; Konishi et al, 2000; Maratos et al, 2001; see chapter 1). To examine if any of these effects were enhanced during retrieval of emotional memories, the old/new contrast was *inclusively* masked with the contrast used to identify valence-independent emotion effects (see below). Effects in the left angular gyrus and left middle temporal gyrus survived this masking, and therefore presumably reflect memory effects which are enhanced when retrieved memories are emotional.

Valence-independent Emotion Effects

To identify valence-independent emotion effects, the contrast between emotional and neutral hits was *exclusively* masked by the two contrasts used to identify valence-specific effects (see below). The results of this contrast are listed in table 5.3a.

Table 5.2 Common old/new effects (inclusive mask of neutral, negative and positive hits – correct rejections). Brodmann areas are approximations based on peak coordinates.

	Region			Peak coordinates			
			Voxels	x	y	z	Peak Z
L	Precuneus	(BA 31)	41	-6	-68	18	4.29
L	Angular gyrus	(BA 39)	40	-46	-68	32	3.64
L	Superior parietal lobule	(BA 7)	49	-34	-64	50	4.29
L	Superior parietal lobule	(BA 7)	22	-26	-60	46	3.59
L	Inferior parietal lobule	(BA 40)	109	-44	-58	40	4.91
L	Posterior cingulate	(BA 31)	68	-4	-56	26	3.37
L	Cingulate gyrus	(BA 31)	5	-10	-44	30	3.39
L	Middle temporal gyrus	(BA 21)	29	-64	-42	-8	3.46
L	Inferior frontal gyrus	(BA 46)	6	-42	32	10	3.49
L	Middle frontal gyrus	(BA 10)	47	-32	50	0	3.97

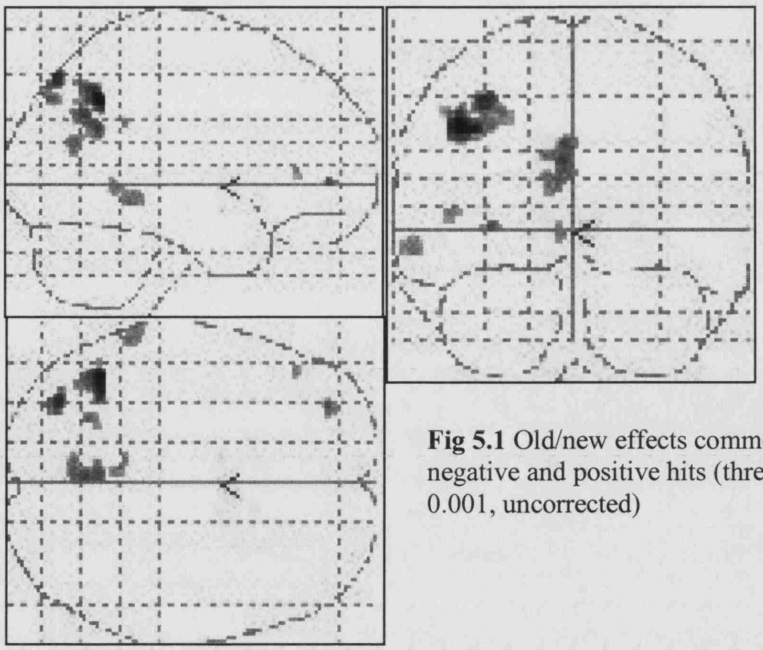

Fig 5.1 Old/new effects common to neutral, negative and positive hits (thresholded at $p < 0.001$, uncorrected)

Table 5.3a Regions showing significant signal increases for emotional vs. neutral hits (exclusively masked with negative-positive and positive-negative hits at $p<0.05$, uc)

	Region		Voxels	Peak coordinates			Peak Z
				x	y	z	
L	Lingual gyrus	(BA 18)	26	-20	-74	-8	5.43
L	Angular gyrus	(BA 39)	35	-44	-68	34	3.68
L	Middle temporal gyrus	(BA 21)	23	-64	-44	-2	3.8
R	Parietal lobe		5	30	-40	30	3.66
L	Insula		5	-48	-26	16	3.25
L	Precentral gyrus		13	-48	-6	24	3.9
L	Amygdala		57	-26	-4	-16	4.66
R	Anterior cingulate	(BA 32)	12	12	44	6	3.3
R	Inferior frontal gyrus	(BA 46)	8	56	28	10	3.35
L	Medial orbitofrontal	(BA 11)	5	-2	46	-20	3.4
L	Medial frontal gyrus	(BA 10)	16	-10	62	10	4.02

Table 5.3b Regions showing significant signal increases for neutral vs. emotional hits

	Region		Voxels	Peak coordinates			Peak Z
				x	y	Z	
L	Middle occipital gyrus	(BA 18)	25	-28	-84	0	3.8
L	Posterior cingulate		7	-14	-52	16	3.68
L	Cerebellum		16	-6	-50	-34	3.97
R	Middle temporal gyrus	(BA 21)	9	40	-6	-28	3.41

A number of these valence-independent effects survived *exclusive* masking with the neutral old/new contrast, suggesting that they might be emotion-specific. These included effects in left amygdala, left lingual gyrus, left insula, right mid- and anterior cingulate, right inferior frontal gyrus, left medial orbitofrontal cortex and medial frontal gyrus (Figs 5.2, 5.3). Regions of the left middle occipital gyrus, left cerebellum, left posterior cingulate and right middle temporal gyrus showed significantly greater haemodynamic responses during recognition of items encoded in neutral vs. emotional contexts (Table 5.3b, Fig 5.4).

Valence-Specific Emotion Effects

Negative hits elicited greater activity than positive hits in a number of regions (table 5.4) including left fusiform, left middle occipital gyrus, bilateral middle temporal gyri, bilateral cuneus and left medial frontal gyrus. Regions in the right precuneus and left inferior parietal lobule were significantly more active for positive vs. negative hits (table 5.5). Additionally, a contrast of positive hits and correct rejections revealed effects in the left parahippocampal region, right hippocampus, and left medial frontal

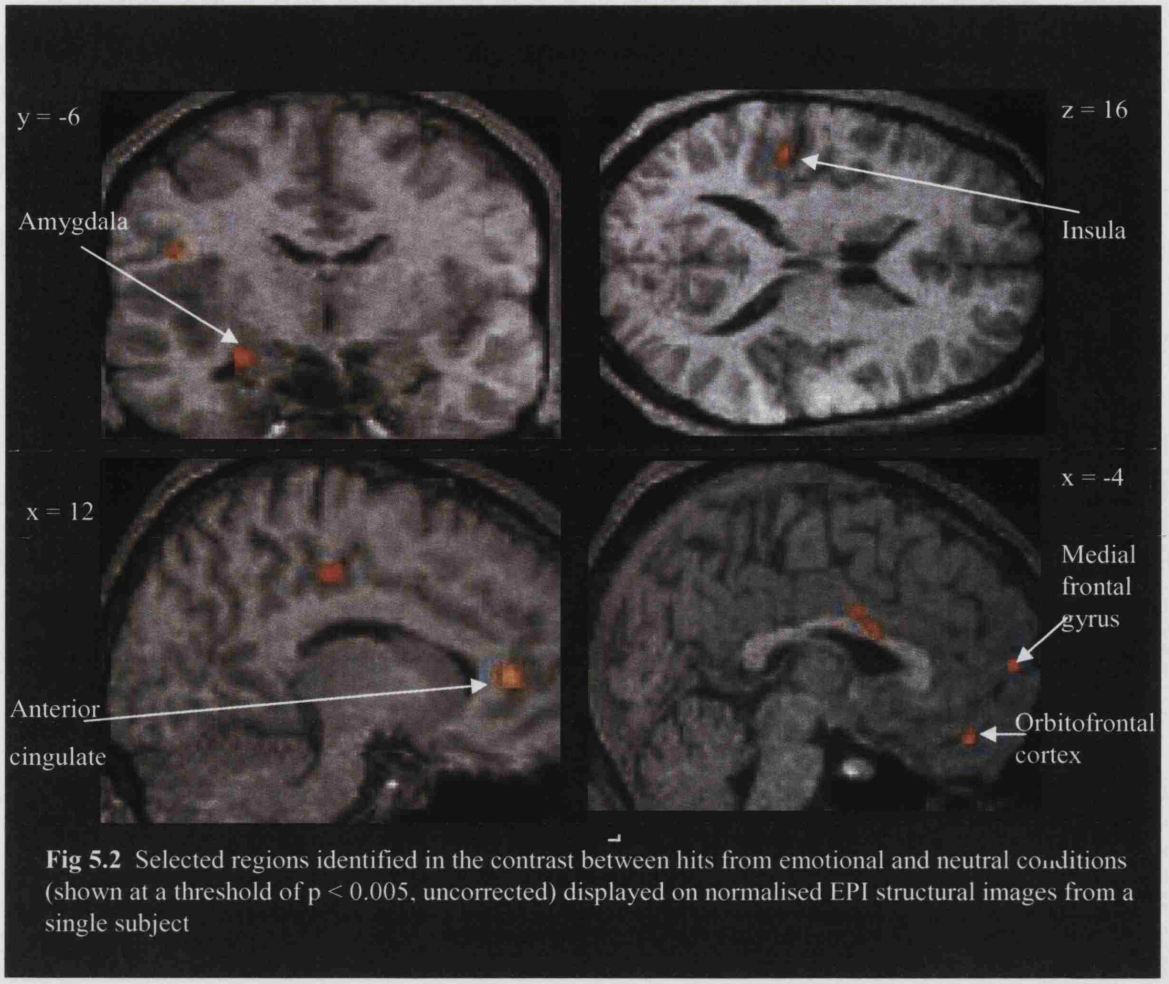

Fig 5.2 Selected regions identified in the contrast between hits from emotional and neutral conditions (shown at a threshold of $p < 0.005$, uncorrected) displayed on normalised EPI structural images from a single subject

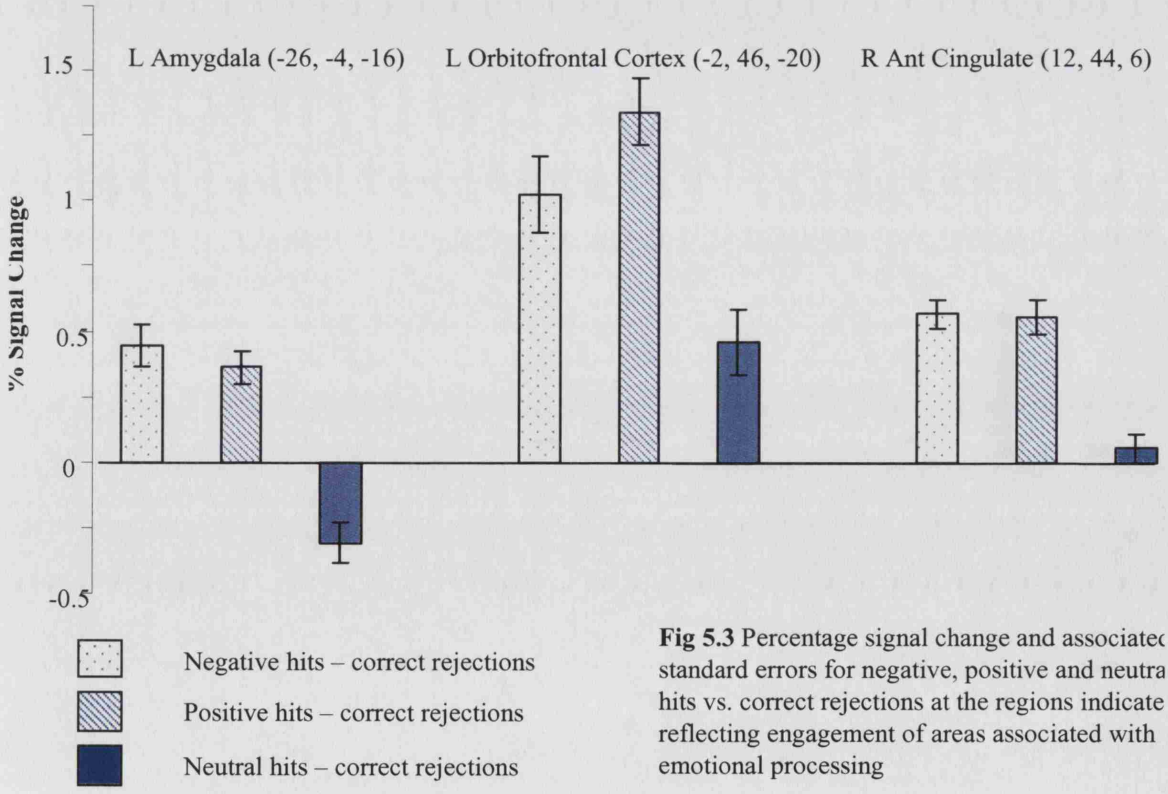

Fig 5.3 Percentage signal change and associated standard errors for negative, positive and neutral hits vs. correct rejections at the regions indicated reflecting engagement of areas associated with emotional processing

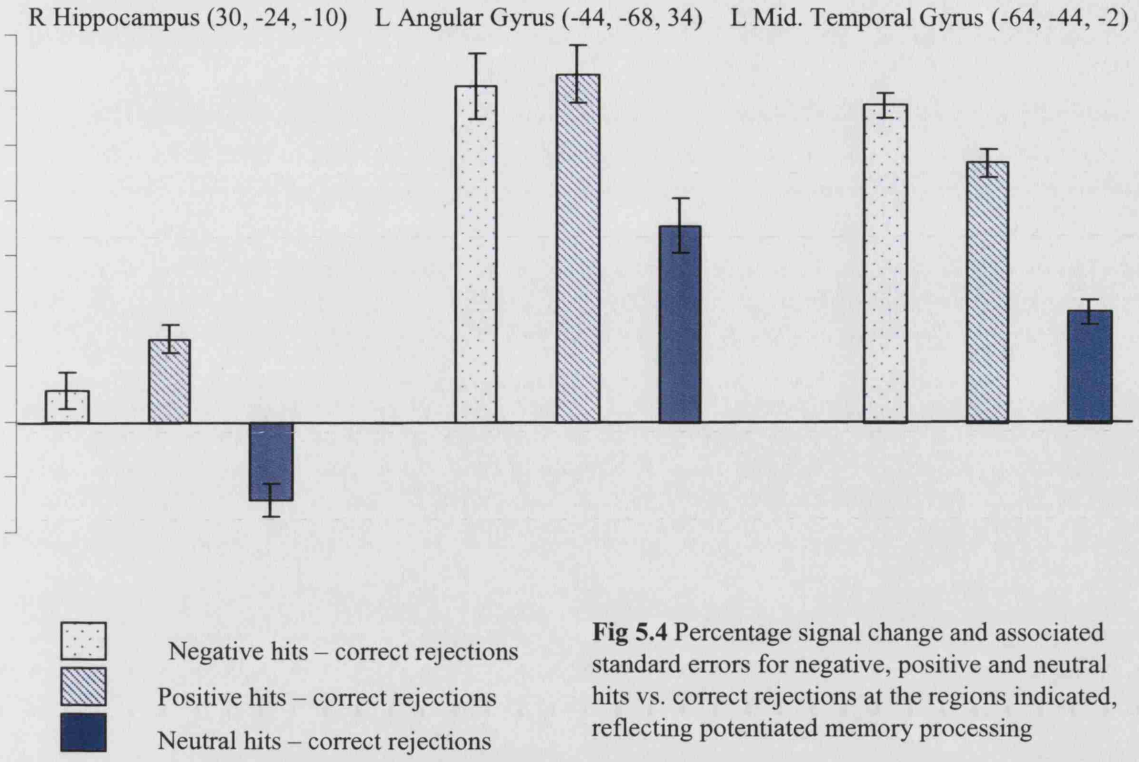

Fig 5.4 Percentage signal change and associated standard errors for negative, positive and neutral hits vs. correct rejections at the regions indicated, reflecting potentiated memory processing

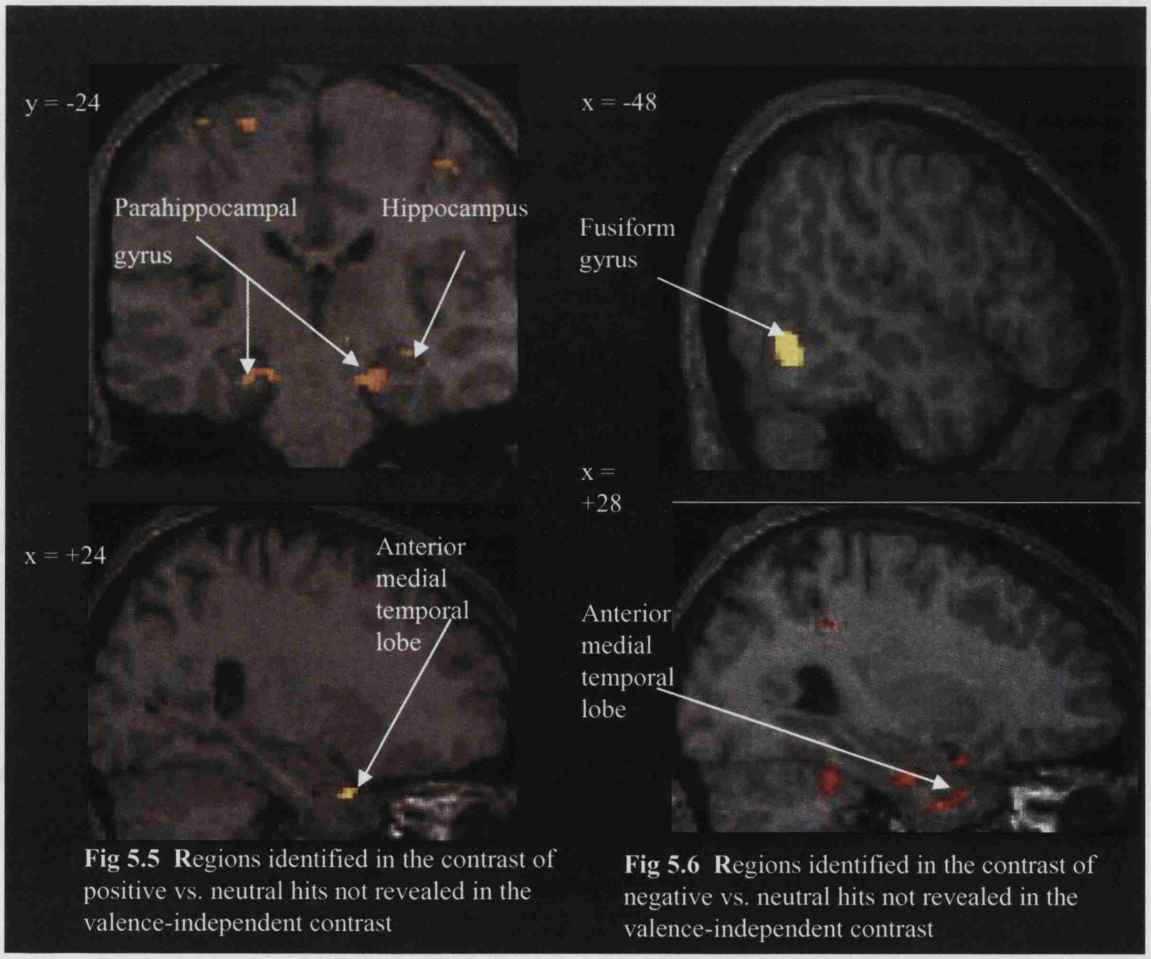

Fig 5.5 Regions identified in the contrast of positive vs. neutral hits not revealed in the valence-independent contrast

Fig 5.6 Regions identified in the contrast of negative vs. neutral hits not revealed in the valence-independent contrast

Table 5.4 Regions showing significant signal increases for negative vs. positive hits

	Region		Voxels	Peak coordinates			Peak Z
				x	y	Z	
R	Cuneus		5	20	-90	8	3.48
L	Cuneus		10	-6	-88	12	3.34
L	Middle occipital gyrus	(BA 37)	31	-50	-66	-8	3.26
L	Fusiform gyrus	(BA 37)	5	-48	-58	-12	3.33
L	Middle temporal gyrus	(BA 21)	8	-64	-42	-4	3.2
R	Middle temporal gyrus	(BA 38)	5	38	6	-36	3.4
L	Medial frontal gyrus	(BA 6)	14	-14	10	50	3.46
L	Medial frontal gyrus	(BA 9)	5	-8	28	30	3.12

Table 5.5 Regions showing significant signal increases for positive vs. negative hits

	Region		Voxels	Peak coordinates			Peak Z
				x	y	Z	
R	Precuneus	(BA 7)	6	16	-68	50	3.27
L	Inferior parietal lobule	(BA 40)	5	-40	-30	30	3.48

gyrus (Fig 5.5), whilst a contrast between negative and neutral hits revealed effects in right parahippocampal gyrus and right anterior temporal lobe (Fig 5.6).

Common Emotional Effects at Encoding and Retrieval

A number of regions identified in the retrieval contrasts also showed effects in a contrast which revealed emotion-related differences in activity during the encoding of those items which were subsequently recognised. Valence-independent effects of

Table 5.6 Regions showing significant signal increases for negative vs. neutral hits (A) and positive vs. neutral hits (B) not revealed in the valence independent contrast

	Region		Voxels	Peak coordinates			Peak Z
				x	y	Z	
(A)							
L	Parahippocampal gyrus	(BA 35)	61	-22	-28	-18	4.09
R	Hippocampus		6	30	-24	-10	3.26
R	Anterior temporal lobe	(BA 28)	12	24	6	-30	4.19
R	Middle frontal gyrus	(BA 9)	7	34	38	36	3.35
L	Medial frontal gyrus	(BA 10)	64	-8	60	2	4.67
(B)							
R	Parahippocampal gyrus	(BA 35)	8	24	-24	-18	3.35
R	Anterior temporal lobe	(BA 34)	160	14	-10	-16	4.59

emotion at encoding are reported in table 5.6 and included visual extra-striate areas, amygdala and prefrontal cortex, regions previously reported to be activated during the viewing or rating of emotional pictures (Lane et al, 1999; Phan et al, 2003; see chapter 2). *Inclusive* masking revealed that overlapping regions of left angular gyrus and left amygdala were more active during both the encoding of the emotional material and subsequent recognition of the associated items.

Overlapping areas of left fusiform gyrus showed effects during both encoding and recognition of items associated with negative backgrounds compared to items associated with either positive or neutral backgrounds.

Table 5.7 Regions showing significant signal increases for encoding of objects in emotional vs. neutral contexts

	Region		Voxels	Peak coordinates			Peak Z
				x	Y	Z	
R	Inferior occipital gyrus	(BA 18)	317	46	-82	-10	4.99
L	Angular gyrus	(BA 39)	64	-40	-70	30	4.21
L	Posterior cingulate	(BA 31)	130	-2	-56	22	4.46
R	Superior temporal gyrus	(BA 13)	144	58	-38	20	5.54
L	Superior temporal gyrus	(BA 22)	169	-56	-26	4	4.96
L	Thalamus		53	-24	-30	2	4.37
R	Thalamus		36	26	-22	8	4.33
L	Amygdala		109	-28	-6	-14	4.69
R	Putamen		46	30	2	10	4.74
L	Middle temporal gyrus	(BA 21)	159	-48	8	-24	4.96
R	Medial frontal gyrus	(BA 11)	117	6	58	-16	4.85
R	Superior frontal gyrus	(BA 10)	25	8	64	16	5.34

Discussion

Behavioural Performance

Items encoded in positively valenced contexts were more likely to be correctly recognised than those encoded in either neutral or negative contexts. This result is consistent with the results of our earlier ERP studies and with another study, which investigated subsequent memory effects for emotional context and pre-experimentally neutral stimuli (Erk et al, 2003). One possibility is that the emotional backgrounds acted to enhance attention during encoding, which may have facilitated the encoding

of the associated neutral items. However, where these backgrounds were extreme and especially attention-grabbing, as for some of the negative backgrounds, attention may have been diverted away from the critical neutral stimuli, thereby impairing encoding. By this argument, moderately arousing backgrounds enhance encoding of associated items, whereas strongly arousing backgrounds might impair it. Such a hypothesis has resonance with a recent study which reported that encoding of arousing, negatively valenced stimuli was associated with amnesia for other items encoded in close temporal proximity to the emotional item (Strange et al, 2003). This may be worth examining further in future, using a wider range of arousal ratings to improve resolution.

A further explanation for the differences in performance for positive and negative conditions is that modulatory neurotransmitters mediating emotion effects on memory may be valence-specific. Thus, the modulatory effects of positive emotion may be principally mediated through increased dopamine release (see Ashby et al, 1999), with negative emotion being principally adrenergic (see Cahill, 1999). Within this framework, enhanced adrenergic drive may direct resources towards processing of an arousing stimulus, dopamine facilitates processing of other environmental elements, or binding of such elements with a positively valenced stimulus.

fMRI Data

The principal aim of the experiment described was to investigate differences between the neural correlates of recognition of items encoded in emotional compared to non-emotional backgrounds. Differences in retrieval-related neural activity are attributable to two potential mechanisms. Firstly, the emotional significance or

valence of the neutral stimuli themselves may be modified by association with emotional backgrounds, giving rise to emotion effects that are independent of any episodic retrieval of associated contextual information. Secondly, the neutral stimuli may act as retrieval cues for the study contexts, with the retrieved information eliciting differential neural activity. We have previously described ERP evidence for each of these types of emotion effect.

Modulation of Episodic Memory

The contrast of hits and correct rejections revealed effects in areas previously reported in event-related studies of recognition memory, including left parietal cortex, posterior cingulate and left prefrontal cortex (see Rugg et al, 2002 for review), as well as in other areas including the angular gyrus and middle temporal gyrus. The angular gyrus (BA 39) and middle temporal gyrus (BA 21) showed old/new effects for all items, but these were significantly greater for emotional than neutral hits. Thus one effect of the emotional manipulation was to increase activity in regions that support episodic retrieval. In particular, the angular gyrus has been identified as being an important component of the semantic memory system (see Price, 2000), and effects here may reflect increased semantic processing of items previously associated with emotional contexts because they are 'tagged' as being significant in some sense.

Emotion effects were also elicited in other structures implicated in episodic memory retrieval, including the hippocampus, parahippocampal areas, and dorso-lateral prefrontal cortex (DLPFC) (see also Maratos et al, 2001). Compared to correct rejections, neutral hits showed a decrease in BOLD signal in the hippocampus (see fig. 5.4), similar to some previous findings in the hippocampus itself (Rombouts et al,

2001) and nearby areas of anterior MTL (Henson et al, 2003). In contrast, emotional hits showed greater BOLD signal than correct rejections. Two distinct possibilities may explain these differences between emotional and neutral hits. Firstly, this effect may reflect that recognition of items encoded in emotional vs. neutral contexts is associated with retrieval of a greater amount of episodic information, which has been reported to correlate with hippocampal activity (Eldridge et al, 2000; Cansino et al, 2002). Secondly, hippocampal effects may relate to incidental encoding activity during the recognition test (see Stark and Okado, 2003): Encoding activity is generally highest for novel stimuli, but items previously associated with emotional backgrounds may be 'tagged' as significant, resulting in increased resources being dedicated to their (re)encoding at the time of test. Such enhanced encoding might result from an amygdala-mediated modulation of hippocampal activity (see McGaugh et al, 1996), both at the time of initial encoding and at the time of retrieval/re-encoding. A similar re-encoding process might explain the enhanced activity in parahippocampal areas, which have previously been reported to show novelty/familiarity responses (Henson et al, 2003), and have also been associated with subsequent memory performance for emotional stimuli in a contextual paradigm (Erk et al, 2003).

Right DLPFC has been linked to post-retrieval monitoring of retrieved information (Henson et al, 1999a, 1999b, 2000). Recognition of items encoded in emotional vs. neutral contexts may be associated with a higher probability of incidental retrieval of episodic information, or with a quantitatively greater amount of information being retrieved, in either case increasing the amount of information to be monitored; alternatively, the same amount of information may be more closely monitored when it has emotional significance (at least when the information is not task relevant; see also

Maratos et al, 2001). Differences have previously been reported in the 'right frontal old/new effect' in an ERP recognition study of words encoded in negative vs. neutral sentences (Maratos and Rugg, 2001) consistent with the present proposal.

Emotion-specific Effects

A number of effects survived exclusive masking with the neutral hits – correct rejection contrast, and they were outside regions associated with retrieval of neutral episodic information. Several effects were valence-independent, including effects in the left amygdala. Before further discussion of these findings, it is worth considering the possible role of the amygdala in this task, and emotional retrieval in general.

Although much less well established than during encoding and consolidation of emotional memory, there is some evidence for a crucial role of the amygdala at the time of retrieval. In rodents, Nader and LeDoux (1999) have shown that reducing dopamine D1 receptor activation in the basolateral amygdala in a second-order fear conditioning paradigm reduces subsequent freezing responses to the second conditioned stimulus, suggesting an impairment in emotional retrieval (see also Greba and Kokkinidis, 2000). Consistent with this view, Seidenbecher and colleagues (2003) have shown increased synchronisation of amygdalar and hippocampal theta rhythms following exposure to previously conditioned stimuli and contexts. Interactions of the amygdala with mnemonic structures during retrieval have also been proposed to account for mood congruency effects in humans (Rolls and Stringer, 2001).

It is also important to consider whether the specific task employed here is likely to be dependent upon the amygdala. Phelps and colleagues (1998) have reported that a

patient with bilateral amygdala damage showed enhancement of memory for neutral words embedded within emotional sentences equivalent to that for controls (see also Phelps et al, 1997; Kensinger et al, 2002 for supporting findings), suggesting that the amygdala may not be critical for emotional source memory in contextual paradigms. However, it should be noted that control subjects in that experiment did not report emotional arousal during sentence generation, and in another experiment the same patient also showed equivalently enhanced memory for emotional words which were not associated with physiological arousal. This suggests that emotion may enhance memory through both arousal-dependent and arousal-independent mechanisms, with only the former dependent on the amygdala (see Phelps et al, 1998). There is no *a priori* reason, therefore, to suspect that retrieval of arousing emotional sources, as in the present experiment, may not recruit amygdala-dependent mechanisms. Further to this, even if the amygdala is unnecessary for reporting whether an item has emotional associations, it may have an important role in reacting appropriately to retrieved information, coordinating physiological and behavioural responses to stimuli with acquired emotional value or retrieved emotional representations.

Other studies of both encoding and retrieval have reported activity in the amygdala. Dolan and colleagues (2000) reported enhanced left amygdala activity during recognition of emotional vs. neutral pictures, while Maratos et al (2001) reported a nearby region in a comparison of neutral words encoded in negatively vs. neutrally valenced sentences (and a trend in the same region for the positive vs. neutral contrast). In addition, Büchel et al (1999) reported effects in left amygdala in response to a negatively-conditioned stimulus (in the absence of an unconditioned stimulus), whilst Phelps and colleagues (2001) observed an enhanced response in this same region to a stimulus which subjects had been informed was associated with the threat

of mild electric shock (no shock was actually experienced). Together, these data suggest that the amygdala is engaged by a variety of emotional memory processes, possibly 'tagging' retrieved memories with representations of their behavioural significance (Weiskrantz,1956).

Valence-independent emotion effects were also evident in insular cortex, a finding also reported by Maratos and colleagues (2001). The insula is most commonly associated with processing of disgust (e.g. Phillips et al, 1997; Calder et al, 2000), but has also been reported in studies of fear conditioning (e.g. Critchley et al, 2002), instructed fear learning (Phelps et al, 2001), and viewing of both positive and negative pictures (Kuniecki et al, 2003). This structure may be preferentially engaged when emotional tasks are cognitively demanding or require internal generation of emotions (see Phan et al, 2002), possibly due to a role in representing emotional states (Damasio et al, 2000). Additional valence-independent emotion effects were found in medial orbitofrontal cortex and medial frontal gyrus. Activity in orbitofrontal cortex (OFC) and ventromedial prefrontal regions has been shown to correlate with individual subject ratings of emotional arousal (Phan et al, 2003) and has been proposed to reflect integration of emotional information derived from an extended emotional circuit (see Krawczyk, 2002). Another brain region showing greater activity for emotional than neutral stimuli was the right anterior cingulate cortex, a region reported to be involved in a number of different processes, including autonomic control (Critchley et al, 2000a; 2000b), conflict monitoring (van Veen et al, 2001), emotion induction (Teasdale et al, 1999), memory retrieval (Cabeza and Nyberg, 2000) and problem solving (Prabhakaran et al, 1997). Activity in this area may index physiological arousal, whether this is induced by emotional or higher cognitive processing.

Valence-specific emotion effects

An extended area of left fusiform gyrus showed enhanced activity associated with negative hits. An overlapping region (though bilateral and more extensive) was reported by Lane and colleagues (1999) during passive viewing of emotional pictures. This effect may result from re-entrant processing enhancing visual processing of emotional stimuli even when, as in this case, this emotionality is only a product of a stimulus' study history (see Dolan, 2002). Positive and negative conditions both showed enhanced activity in anterior temporal lobe, previously suggested by Dolan and colleagues (2000) to reflect a state of emotional memory retrieval. That the areas of anterior temporal lobe differed for positive and negative memories might reflect adoption of valence-specific retrieval strategies, though such a proposal is only tentative.

Common Emotion Effects at Encoding and Retrieval

Some brain regions showed significant emotion effects during both encoding and retrieval. As noted earlier, the left angular gyrus is involved in semantic processing (see Price, 2000), suggesting that semantic assessment of stimuli may be enhanced when those stimuli are tagged as being behaviourally significant in some way, due either to current or previous association with emotional stimuli. Overlapping regions of left amygdala also showed enhanced activity during both encoding and retrieval of items associated with emotional backgrounds. Similar areas have been reported in other encoding tasks, and related to subsequent memory performance (Hamann et al, 1999; Erk et al, 2003). It may be that the amygdala is important for representing

emotional information whether this comes from external or internal sources (see also Pitkanen et al, 1997; Phelps et al, 2001).

It should be noted that contrasts included only subsequently remembered items, so as to obviate effects arising from differences in subsequent memory across conditions. This does, however, restrict the present findings to successful encoding and retrieval, and processing of subsequently forgotten items might be rather different.

The above discussion is predicated on the assumption that contrasts between conditions arise solely as a result of the emotional differences between backgrounds. However, other possibilities exist – in general, emotional backgrounds were more arousing, more interesting and more novel than their neutral counterparts. While a previous ERP study (chapter 4, experiment 2) suggests that the effects cannot be solely attributed to non-emotional differences, the different sensitivities of ERP and fMRI do make it possible that some effects in the present experiment do not genuinely reflect differences in emotional valence and arousal.

Another issue is the possibility that formation of associations between backgrounds and paired objects may have been easier when there was an obvious or natural connection, which may have been more common in the neutral encoding condition, or when contexts were more distinctive and unusual, as many of the emotional contexts were. This issue will be revisited later.

As to the valence-specific effects, these might arise from differences in recognition performance or confidence (in the case of positive>negative effects) or as effects of arousal (as negative stimuli were, on average, more arousing than their positive counterparts) as well as differences between the processing of negative and positive emotions. Whilst high-threshold arousal effects could have contributed to emotion-

specific effects, it should be noted that they do not overlap with the valence-independent emotion effects, which partly reflect arousal differences between emotional and neutral stimuli. Though contrasts were limited to correctly recognised items, differences in confidence between conditions cannot be ruled out as contributing to the effects reported here, and it may be of interest in the future to examine the effects of emotion on retrieval processing of items recognised with varying degrees of confidence.

Summary

Brain activity associated with recognition of pictorial stimuli was shown to be modulated as a function of the emotional context associated with such stimuli during encoding, in accordance with previous ERP evidence (chapter 4) and a fMRI study using a similar approach, but with verbal material (Maratos et al, 2001). The effects reported in this study are qualitatively similar to those elicited by neutral words studied in emotional sentences (Maratos et al, 2001). While some differences between the reported activations can be observed, the principal effects of emotion in engaging an extended emotional circuit, as well as modifying retrieval and post-retrieval processing, appear to be common across verbal and non-verbal modalities.

The various changes in processing reported here were elicited in a task where the emotional manipulation has no relevance to the retrieval task, and one interesting question relates to whether some effects arise from automatic and obligatory engagement of processes which could be engaged for neutral memories where contextual information is task-relevant. This issue is addressed in the next chapter.

Chapter 6: Event-Related Potential Correlates of the Successful and Unsuccessful Retrieval of Emotional Context

Introduction

The experiments described in the two previous chapters have demonstrated that encoding items in emotional contexts can lead to improvements in recognition memory and engagement of additional cognitive processing during retrieval. However, a number of important questions remain about these findings. Firstly, if recognition performance is supported by qualitatively distinct neural processes of recollection and familiarity (see chapter 1), does emotion have differing modulatory effects on these processes?

Secondly, the effects of emotion observed in the earlier experiments reflect engagement of processes by task-irrelevant information about the encoding context. It is of interest to determine whether these effects are attenuated or not when contextual information is task relevant. If the processes engaged by items from emotional contexts reflect specific emotional retrieval processes, or emotional responses to the retrieved material it would be predicted that activity would be unchanged by making contextual information task relevant. Furthemore, it might be expected that these emotion effects would only be observed under conditions where emotional context was successfully retrieved (rather than cases where recognition was based on an acontextual sense of familiarity). Alternatively, the previously observed emotion effects might reflect something such as the salience of retrieved information. Retrieved emotional information tends to be salient, whether or not it is relevant to the current task, whereas neutral information is only likely to be salient when it is task-relevant. Therefore, if the previously observed effects do indeed reflect some salience

effect then we would predict an attenuation of emotional/neutral differences when neutral contextual information is task-relevant. The present experiment used a source memory task in an attempt to address these issues.

Methods

Stimulus materials, list construction and ERP recording were identical to those used for experiment 1 (see chapter 4), and will not be repeated here.

Subjects

Nineteen right handed young adults (age range 18-33 years, mean 23.2) were employed as subjects and remunerated at the rate of £7.50/hour. All subjects reported good health and had no history of neurological or psychiatric illness. 1 subject was excluded from the final analysis due to inadequate behavioural performance. Of the 18 subjects contributing data, 11 were female. This study was approved by the joint UCL/UCLH ethics committee.

Study Procedure

In the study phase, stimuli were presented in the centre of a colour computer monitor. The background was presented first, alone on the screen for 3000ms. During this time subjects were asked to make a verbal rating of the backgrounds emotional valence, using a 7 point Likert scale, ranging from -3 (very unpleasant) to +3 (very pleasant). Individual subject ratings were used in conjunction with the normative data to assign the stimuli to the experimental categories for that subject.

After 3000ms the critical object was superimposed centrally upon the background and subjects asked to imagine a connection between background and object, which was made covertly. The object and background were presented together for 5000ms, and the screen was then blanked for 750ms before presentation of the next background. Six practice trials were given prior to the study proper, with the subjects asked to describe the connections they had made explicitly (unlike in the experiment proper) to ensure understanding of the task. Rest breaks were given after every 62 background/ object pairs, the first two stimuli of each subphase being neutral filler items.

Test Procedure

The test phase followed the study phase after a delay of five minutes, a serial subtraction task being employed to obviate rehearsal. A white asterisk was presented against a black background for 500ms to cue preparation, after which test stimuli were displayed for a duration of 750ms. Subjects had to make an old/new response judgement as quickly and accurately as possible.

750ms after the screen blanking, a question mark character was displayed for 2000msec to cue the second, source response. The requirement was to indicate the valence of the encoding context with which the item had been associated at study. Subjects performed this task with the forefinger and middle finger of each hand resting on separate microswitches, these switches indicating that the object had been seen in a 'negative', 'neutral' or 'positive' context, or that they could not remember the context with which an object had been presented. This task can be considered a hybrid between R/K and source memory tasks. It has an advantage over R/K tasks in providing an objective measure of successful recollection (though one limited to a specific aspect of the previous experience), whilst avoiding the forced choice typical

in source memory tasks. This aims to reduce the amount of guessing, and thus the number of trials in the source hit condition which are not associated with genuine episodic retrieval. The hand required for recognition and source judgements was counterbalanced across subjects. Between each stimulus a white fixation cross on a black background appeared for 1000ms, giving a stimulus onset assynchrony of 4500ms.

EEG was recorded as described previously (chapter 3b; chapter4) and ERPs formed for correctly rejected new items and correctly recognised old items associated with each valence category (positive, negative and neutral) and attracting correct source judgements. Additionally, 'source miss' ERPs were formed for correctly recognised items either attracting inaccurate source judgements or 'don't know' judgements, separated according to whether they had been paired with a neutral or emotional (collapsed across positive/negative) context at study. Collapsing across inaccurate source and 'don't know' trials, and across positive/negative was necessary to ensure reasonable SNR for the source miss ERPs, as there were relatively few trials in some of categories. Subjects were excluded if the number of trials contributing to any ERP waveform of experimental interest fell below 16 trials.

Results

Behavioural Data

Mean ratings (SD in parentheses) for each class of background were (from –3 to 3) - neutral: 0.06 (0.14); positive: 1.92 (0.27); negative: -2.12 (0.39). Both positive and negative items differed significantly from neutral item ratings (both $F>100$, $p<0.001$), whilst the difference between negative and neutral items was greater than that

between positive and neutral [$F(1,17) = 7.144$, $p<0.0025$]. This was a similar pattern to that seen in pre-experimental assessment of material, the IAPS ratings and the experiments described earlier.

Table 6.1 and figure 6.1a show hit rates for the original old/new recognition decision, and the correct rejection rates. One-way ANOVA of these data showed a main effect of condition [$F(2.3,39.5) = 18.51$, $p < 0.001$]. Planned pairwise t-tests showed that there were more correct responses to new objects than any class of old object (all $t_{17} > 2.2$, $p < 0.05$). There were also significantly more correct responses to old items encoded with a positively valenced context than objects associated with either negative ($t_{17} = 3.83$, $p < 0.005$) or neutral ($t_{17} = 4.95$, $p < 0.001$) backgrounds. Mean proportion of hits for objects associated with neutral or negative backgrounds did not differ reliably. Further analysis revealed that recognition accuracy correlated with individual valence ratings for the positive contexts ($X^2 = 0.570$, $p < 0.01$), with accuracy improving for items associated with contexts rated as being more positive. No such correlation was found between recognition accuracy and negative valence ($X^2 = 0.07$).

Table 6.1 Mean recognition accuracies, source accuracies and RTs (standard deviations in parentheses).

	Neutral	Negative	Positive	New
Recognition Accuracy	0.80 (0.07)	0.83 (0.08)	0.88 (0.05)	0.92 (0.04)
Proportion of correct source judgements	0.52 (0.05)	0.68 (0.10)	0.65 (0.10)	-
Proportion of 'Don't know' judgements	0.43 (0.05)	0.24 (0.07)	0.28 (0.08)	0.86 (0.02)
Proportion of source misattributions	0.05 (0.03)	0.08 (0.04)	0.07 (0.03)	0.14 (0.03)
RT (msec)	1204 (382)	1187 (399)	1132 (277)	1018 (216)

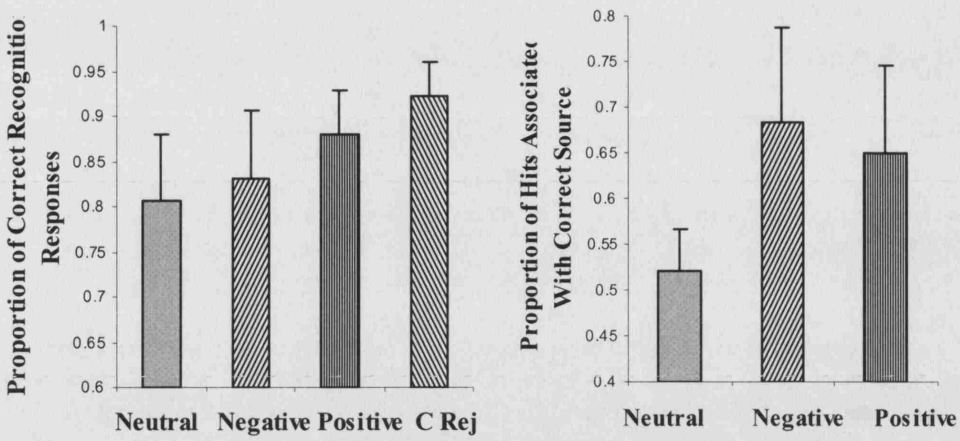

Fig 6.1 Histograms showing the proportion of items from each item category which were correctly classified as old or new (a) and the proportion of recognised items attracting correct source judgments (b).

The proportions of hits attracting correct source judgements in each valence category are shown in table 6.1 and figure 6.1b. Guessing was discouraged by inclusion of a 'don't know' response at source judgement. An ANOVA comparing the proportion of source hits revealed a significant effect of valence [$F(1.5,25.5) = 26.05$, $p<0.001$]. Planned t-tests showed that, compared with items encoded in a neutral context, those encoded in either negative ($t_{17} = 5.71$, $p < 0.001$) or positive ($t_{17} = 5.19$, $p < 0.001$) contexts were more likely to attract a correct source judgement. The difference in proportion of positive and negative source hits was not significant. Further analysis also identified a correlation between the extremity of the valence scores and the probability of attracting a correct source judgement ($X^2 = 0.530$, $p < 0.01$), which was independently significant for both positive ($X^2 = 0.72$, $p < 0.01$) and negative ($X^2 = 0.473$, $p < 0.01$) contexts.

RTs differed reliably across conditions [$F(2.3,38.9) = 3.827$, $p < 0.05$], but did not differ according to valence. Planned t-tests showed that subjects were faster to reject new items than they were to correctly recognise any class of old item (all $t_{17} > 2.5$, $p < 0.05$).

ERP Data

The mean number of trials (range in parentheses) contributing to the average ERPs for each correct response type were – correct rejections, 45 (17 – 75), neutral source hits, 19 (16 – 23), -ve source hits, 26 (16 – 39), +ve hits, 24 (16 – 37), neutral source misses (collapsed over source incorrect and don't know) 18 (16 – 21), emotional source misses (collapsed over source incorrect/don't know and positive/negative) 20 (16 – 30). Visual inspection and an ANOVA comparing waveforms to positive and negative source hits revealed no significant difference in any latency region (all [$F(1,17) < 0.5$, $p > 0.5$) and therefore these were collapsed to form a single emotional hit condition. Further waveforms were produced for neutral source misses by collapsing across those correctly recognised items associated with neutral context attracting either a 'don't know' response or an incorrect source judgement, and for emotional source misses collapsing across both positive and negative and source unknown and incorrect. These waveforms are shown for selected electrode sites in figures 6.2 and 6.3.

Waveforms began to diverge from about 300ms after stimulus onset. All ERPs associated with recognised items were positive relative to the waveform for correct rejections; this old/new difference was larger where recognised items had received a correct source judgement and was initially most pronounced over left parietal and temporal regions, shifting with time to become greatest over right frontal scalp.

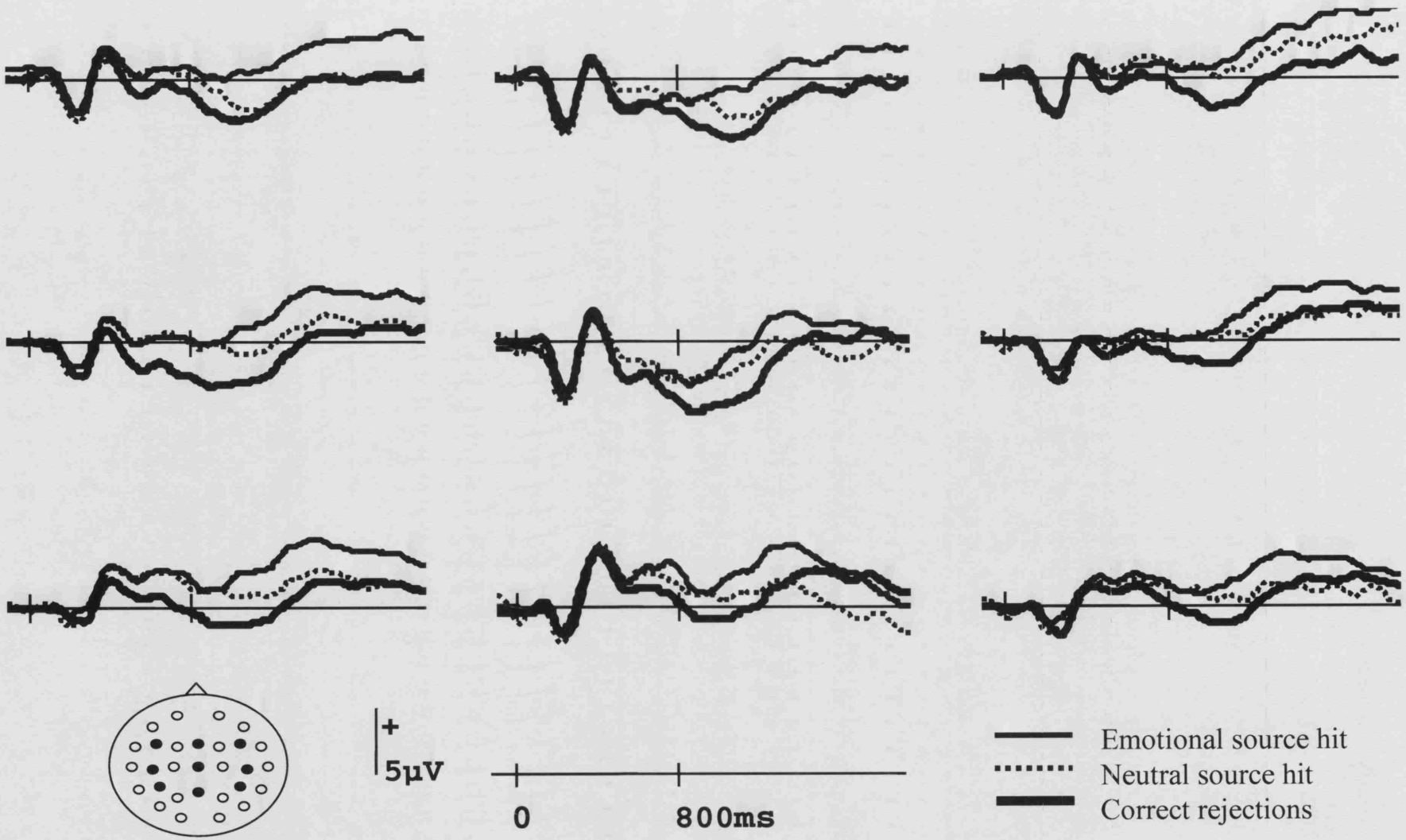

Figure 6.2 Grand average ERP waveforms elicited by recognised items attracting correct source judgements. Negative and positive source hits have been collapsed into a single set of waveforms. Sites as depicted on the insert.

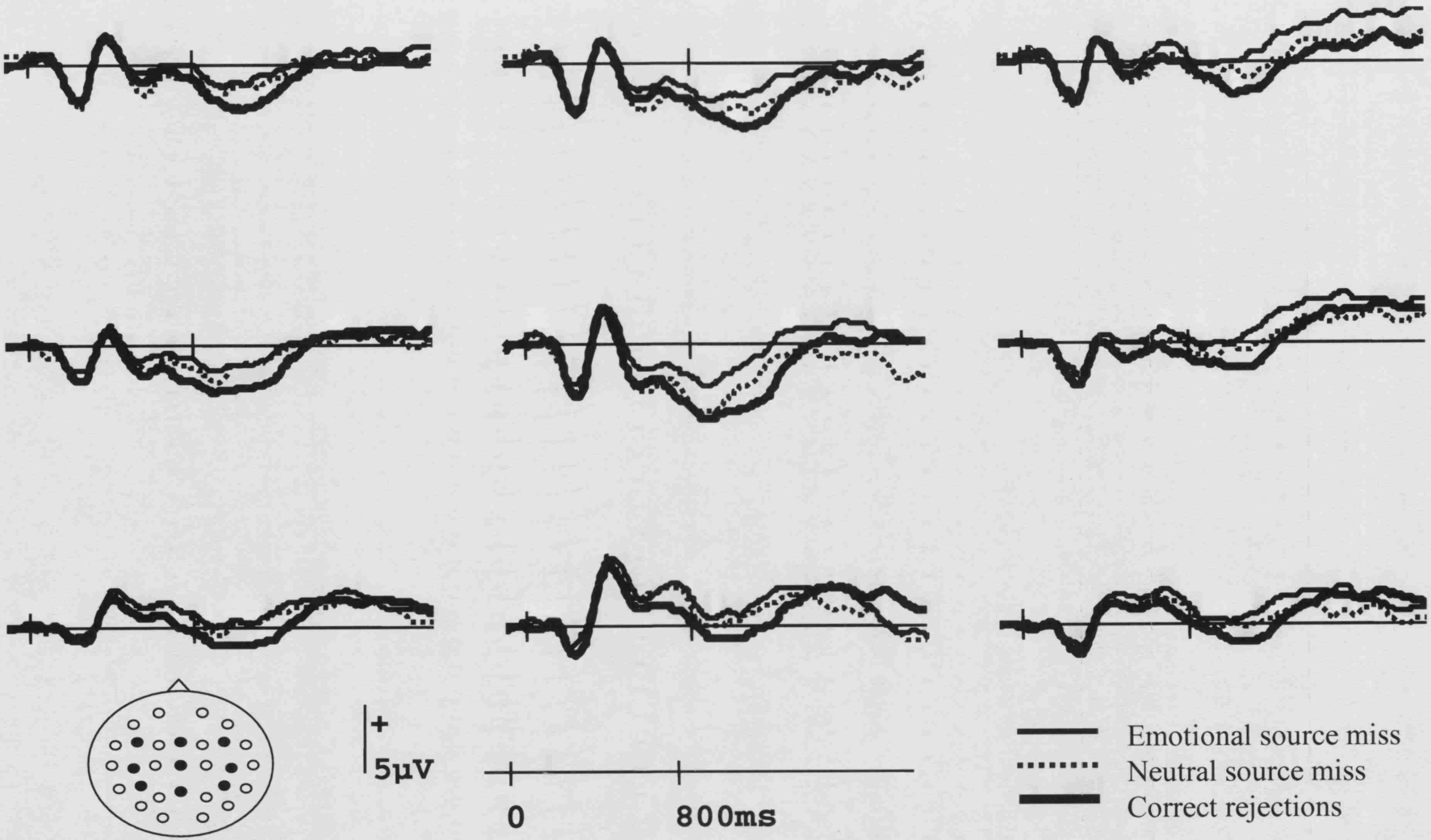

Figure 6.3 Grand average ERP waveforms elicited by recognised items not attracting correct source judgements. Negative and positive source hits have been collapsed into a single set of waveforms. Sites as depicted on the insert.

The waveform elicited by emotional source hits diverged from its neutral counterpart at around 800ms after stimulus onset. A widespread positive difference was observed, largest in left temporal and central regions, but also present over left parietal, right temporal and central and bilateral frontal scalp. Differences as a function of valence were also present for the recognised items not attracting correct source judgements, emotional source misses showing greater positivity than neutral source misses. The difference between emotional and neutral source misses was focussed over right central and frontal electrode sites, and was less widespread than the emotion-related difference between source hit waveforms.

ERPs were quantified by measuring mean amplitudes in the same 5 latency regions as in experiments 1 and 2 (chapter 4). As in those experiments, separate analyses were conducted to assess between-condition differences in amplitude and scalp topography.

Where ANOVA demonstrated significant effects that involved item type prompted subsidiary analyses to contrast separately neutral hits versus correct rejections (neutral old/new effects), emotional hits versus correct rejections (emotional old/new effects), and emotional versus neutral hits (emotion effects). Analyses were performed separately for source hit and miss trials, with further analysis performed directly comparing these trial types.

Source Hits

Mean Amplitude Analyses

The outcomes of the overall ANOVAs are shown in Table 6.2 for each latency region. In every region, reliable effects involving the factor of item type were present. Also

shown in the table are the results of the subsidiary ANOVAs for each latency region. We elucidate these below, discussing the neutral old/new effects, emotional old/new effects and emotional source hit effects, respectively.

Neutral old/new effects

As shown in Table 6.2, a main effect of item type was found for the first 4 latency regions, reflecting in each case a greater positivity for ERPs to neutral source hits. The interactions found for all analyzed latency regions among item type, hemisphere, and AP location reflect the fact that the old/new effects were distributed unevenly over the scalp in each case. These effects are left lateralized early in the epoch, but demonstrate a pronounced right frontal maximum subsequently (Figs 6.2, 6.4).

Emotional old/new effects

A main effect of item type was accompanied by interactions with the factors of hemisphere and AP location in all latency regions analyzed. For the 300- to 500-msec and 500- to 800-msec regions, these interactions reflect the greater size of the old/new effects over the left temporo-parietal scalp. In the subsequent latency regions, these effects are joined by a second maximum over the right fronto-temporal scalp (see Figures 6.2; 6.4).

Emotion effects

In contrast with experiment 1 (chapter 4), emotion effects in the 300- to 500-msec latency region failed to reach significance in the ANOVA utilizing the 18 lateral sites

Latency Region	300 – 500ms	500 – 800ms	800 - 1100ms	1100 - 1400ms	1400 - 1900ms
Source hits/ CR					
Item type (IT)	F(2,33.2) = 9.57; p = 0.001	F(1.3,22.4) = 17.98 p < 0.001	F(1.9,33) = 42.86 p < 0.001	F(1.3,22.7) = 113.5 p < 0.001	F(1.8,30.1) = 33.45 p<0.001
IT x HM	F(1.9,31.7) = 8.64 p < 0.005	F(1.7,29.2) = 8.96 p = 0.001	F(2,33.2) = 8.15 p = 0.001	-	-
IT x HM x AP x ST	F(4.5,76.7) = 2.77 p < 0.05	F(3.5,58.7) = 4.08 P < 0.01	F(3.6,60.4) = 6.57 p < 0.001	F(3.2,54.2) = 6.57 p = 0.001	F(2.1,35.4) = 5.89 p < 0.01
Neutral source hit vs. CR					
Item type (IT)	F(1,17) = 5.55 p < 0.05	F(1,17) = 28.45 p < 0.001	F(1,17) = 29.31 p < 0.001	F(1,17) = 17.46 p < 0.001	-
IT x HM	F(1,17) = 5.55 p < 0.005	F(1,17) = 9.56 P < 0.01	-	-	-
IT x HM x AP	F(1.6,27.2) = 18.03 p < 0.001	F(1.2,20.1) = 8.26 P < 0.01	F(1.8,30.1) = 15.12 p < 0.001	F(1.8,30.8) = 17.46 p < 0.001	F(1.9,31.8) = 31.79 P < 0.001
IT x HM x AP x ST	F(2.9,49.4) = 3.33 p < 0.05	F(1.9,32.6) = 4.92 P < 0.05	F(2.6,44.1) = 8.23 p < 0.001	F(2.6,43.7) = 8.60 p < 0.001	F(1.5,24.8) = 7.93 P = 0.005
Emotional source hit vs. CR					
Item type (IT)	F(1,17) = 21.66 p < 0.001	F(1,17) = 20.15 p < 0.001	F(1,17) = 73.73 p < 0.001	F(1,17) = 134.22 p < 0.001	F(1,17) = 59.62 P < 0.001
IT x HM	F(1,17) = 10.77 p < 0.005	F(1,17) = 18.48 p < 0.001	F(1,17) = 12.59 p < 0.005	-	-
IT x HM x AP	F(1.5,25.6) = 21.82 p < 0.001	F(1.1,18.3) = 15.91 p = 0.001	F(1.6,27.8) = 19.70 p < 0.001	F(1.6,27.3) = 23.36 p < 0.001	F(1.7,29.3) = 20.01 P < 0.001
IT x HM x AP x ST	F(2.8,47.9) = 3.92 p < 0.05	F(3.2,54.9) = 7.65 p < 0.001	F(3.2,54.8) = 11.94 P < 0.001	F(2.2,36.9) = 8.36 p = 0.001	F(1.9,32.6) = 6.58 P < 0.005

Emotional vs. neutral hits					
Item type (IT)	-	-	F(1,17) = 16.96 P = 0.001	F(1,17) = 47.10 p < 0.001	F(1,17) = 62.65 P < 0.001
IT x HM	-	-	F(1,17) = 11.62 P < 0.005	F(1,17) = 22.35 p < 0.001	F(1,17) = 5.42 p < 0.05
IT x AP	-	F(1.1,19.3) = 5.08 P < 0.05	-	-	-

Table 6.2. F-values, degrees of freedom and probabilities associated with main effects and interactions at the lateral electrode sites indicated in figure 4.1 for the 5 examined latency regions. Abbreviations – IT = item type, HM = hemisphere, AP = anteroposterior position, ST = lateral site.

selected a priori. However, an ANOVA on data from temporal/central and parietal electrodes revealed a main effect of item type, [$F(1,17) = 5.07$, $p < .05$]. Emotion effects were also present in the 500- to 800-msec latency region, in the form of an interaction of item type with AP position. This reflected a small, but significant, amplitude difference most evident at right lateral sites, with emotional source hits being more positive-going than neutral source hits at right lateral parietal and temporal sites, but not at right frontal sites [Item Type x AP interaction, $F(1.2,20.8) = 4.35$, $p < .05$]. Apparent amplitude differences at midline sites in this latency region were not significant. In the 800- to 1100-msec latency region, the large differences between waveforms were reflected in a main effect of item type, with emotional source hits eliciting the more positive-going waveforms. The emotion effects remained significant until the end of the recording epoch. In the latter three latency regions (800–1100, 1100–1400, and 1400–1900 msec), the item type effects interacted with hemisphere, reflecting their tendency to be left lateralized (see Figure 6.5). It should be noted that the pattern of results over right frontal scalp in these latency regions suggest that the emotional effects were additive with the right frontal effect, but did not modulate this effect itself.

Topographic Analyses

An initial ANOVA, employing the factors of site, the five latency regions, and emotion, contrasted the scalp distributions of the old/new effects elicited by each class of source hit (see Figure 6.4). The ANOVA revealed a significant interaction between all three factors, $F(6.2,104.7) = 2.82$, $p < .05$. Subsidiary ANOVAs, conducted separately on the data from each latency region, revealed no significant differences in scalp topography prior to 1100 msec poststimulus. As revealed by item type by

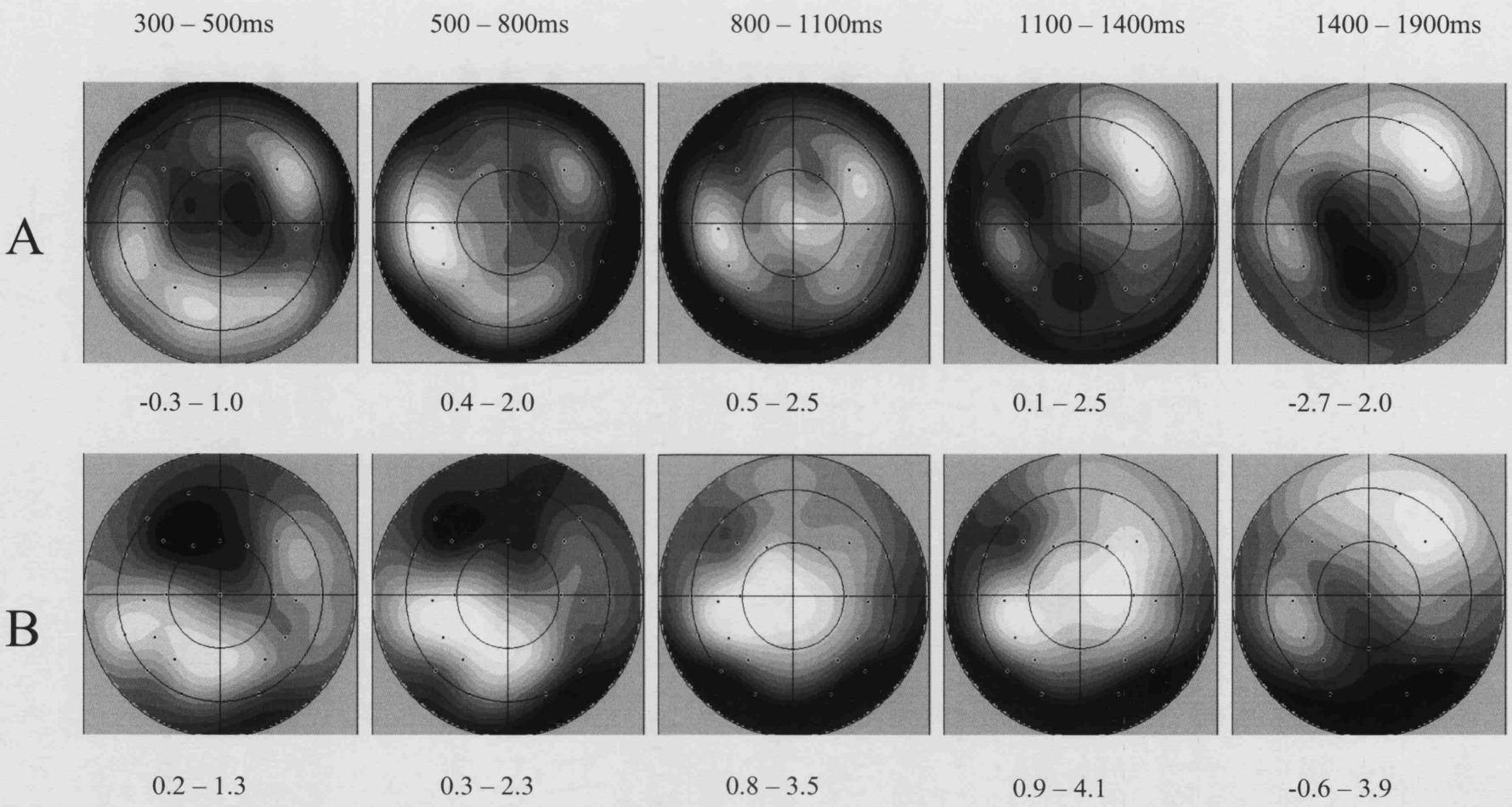

Figure 6.4 Spherical spline maps showing scalp distributions of the old new/effects associated with recognition of items encoded in neutrally (A) and emotionally (B) valenced contexts in the latency regions shown. Each map is proportionately scaled between the extremes of the depicted effect (values in μV given below in each case).

electrode site interactions, the topographies of the two effects differed thereafter, [$F(4.3,73.2) = 9.18$, $p < .001$], and [$F(3.5,59) = 7.04$, $p < .001$], for the 1100- to 1400-msec and 1400- to 1900-msec latency regions, respectively.

A second set of subsidiary ANOVAs examined the topographies of the neutral and emotional old/ new effects separately as a function of latency region. Consistent with the analyses of the raw amplitude data, both ANOVAs revealed significant interactions between electrode site and latency region, reflecting in each case a shift with time from a left temporo-parietal toward a right frontal maximum [neutral: $F(5.9,100.1) = 3.38$, $p = .005$; emotional: $F(5.7,96.5) = 8.46$, $p < .001$, respectively].

Source misses

Mean Amplitude Analyses

Results for the overall ANOVAs are shown for each latency region in table 6.3. In all but the first latency region, reliable effects involving the factor of item type were found. Table 6.3 also shows the outcomes of subsidiary ANOVAs for each latency range, performed separately to examine neutral old/new effects, emotional old/new effects and emotional source miss effects.

Neutral old/new effects

As shown in table 6.3, old/new effects elicited by neutral source misses were first present in the 500-800ms latency range, in the form of an interaction with AP position. This interaction reflected greater old/new differences over parietal compared to frontal regions. Between 800-1100ms there was a main effect of item type, with old items eliciting more positive-going ERPs. An item type x AP

interaction reflected that this effect was larger over the parietal than the frontal scalp. No effects involving item type were significant after 1100ms.

Emotional old/new effects

Emotional old/new effects were first evident between 500-800ms post-stimulus in the form of 2 separate interactions involving item type, with hemisphere and AP position respectively. These interactions reflected the tendency of old/new effects to be maximal over the left parietal scalp. In the 800-1100ms and 1100-1400ms latency regions, ERPs to emotional source misses were again more positive than those to new items. In the 1100-1400ms and 1400-1900ms latency regions 3-way interactions between item type, hemisphere and AP position, reflected the right frontal distribution of the late emotional source miss effects.

Emotional effects

Reliable differences between the ERPs to the emotional and neutral source misses first emerged in the 800-1100ms latency region, as items associated with emotional backgrounds elicited greater postivity than did neutral source misses. These differences were present for the remainder of the recording epoch, and showed interactions with both hemisphere and hemisphere x AP position, reflecting a particular preponderance of these effects over right frontal scalp.

Latency Region	500 - 800ms	800 - 1100ms	1100 - 1400ms	1400 – 1900ms
Source misses/ CR				
Item type (IT)	-	F(1.6,27.5) = 15.42 p < 0.001	F(2,33.5) = 14.90 p < 0.001	-
IT x HM x AP	F(2.6,47.3) = 3.56 p < 0.05	F(2.0,34.8) = 4.27 p < 0.05	F(2.3,38.7) = 9.19 p < 0.001	F(2.0,34.8) = 8.63 P = 0.001
Neutral source miss vs. CR				
Item type (IT)	-	F(1,17) = 29.31 p < 0.001	-	-
IT x AP	F(1.1,18.5) = 18.98 p < 0.001	F(1.7,29.0) = 5.66 p < 0.05	-	-
Emotional source hit vs. CR				
Item type (IT)	-	F(1,17) = 28.79 p < 0.001	F(1,17) = 26.28 p < 0.001	-
IT x HM	F(1,17) = 27.74 p < 0.001	-	-	-
IT x AP	F(1.5,25) = 9.40 p < 0.005	-	-	F(1.2,20) = 12.74 P = 0.001
IT x HM x AP	-	-	F(1.3,22.3) = 17.42 p < 0.001	F(1.3,21.8) = 14.86 P < 0.001
Emotional vs. neutral SM				
Item type (IT)	-	F(1,17) = 4.65 P < 0.05	F(1,17) = 13.72 p < 0.005	F(1,17) = 14.43 P = 0.001
IT x HM	-	F(1,17) = 8.61 P < 0.01	F(1,17) = 7.67 p < 0.05	F(1,17) = 7.22 p < 0.05
IT x HM x AP	-	F(1.2,20.1) = 5.73 p < 0.05	F(1.6,27.7) = 11.82 p < 0.001	F(1.8,31.4) = 4.11 p < 0.05

Table 6.3. F-values, degrees of freedom and probabilities associated with main effects and interactions at lateral electrode sites for source miss trials. Abbreviations – IT = item type, HM = hemisphere, AP = anteroposterior position, ST = lateral site.

Topographic Analyses

An ANOVA comparing the scalp topographies of the emotional and neutral source misses in the two latency region where ERPs to these items both differed from those to correct rejections (500 - 800ms and 800 - 1100ms) failed to reach significance.

Comparison of Emotional Source Hits and Source Misses

A series of analyses directly contrasting the ERPs elicited by emotional source hits and source misses addressed the question of whether source accuracy modulated emotion effects on retrieval. ANOVAs for the analysis of amplitude and topographic differences were performed in a similar manner to those described above.

Mean Amplitude Analyses

Direct comparison of the amplitudes of ERPs to emotional source hits and source misses showed that source hits elicited significantly more positive ERPs than did source misses in all 5 latency regions [min. $F(1,17) = 4.65$, max. $p < 0.05$]. In the first 4 latency regions item type interacted with hemisphere and AP position, reflecting the fact that the greatest differences were seen over left temporo-parietal scalp. In the last latency region, item type interacted with hemisphere alone, with the differences between these two classes of item being larger over left than right scalp.

Topographic Analyses

Comparisons were done between the effects of emotion on source hits (emotional – neutral source hits) and the effects of emotion on source misses (emotional – neutral

source misses) for the three latency regions in which emotion effects were present for both source hit and source miss trials. Use of a subtraction contrast reduced the risk that any differences seen between conditions were due to factors such as the total amount of information retrieved from memory. The scalp distributions of these effects are shown in figure 6.5. ANOVAs revealed significant source accuracy x site interactions (revealing differences in topography) during the 1100-1400ms [$F(2.5,42.6) = 6.16$, $p < 0.005$] and 1400-1900ms [$F(2.7,46.2) = 4.25$, $p < 0.05$] regions, implying that the effects of emotional context may be modulated by the degree of emotional information retrieved.

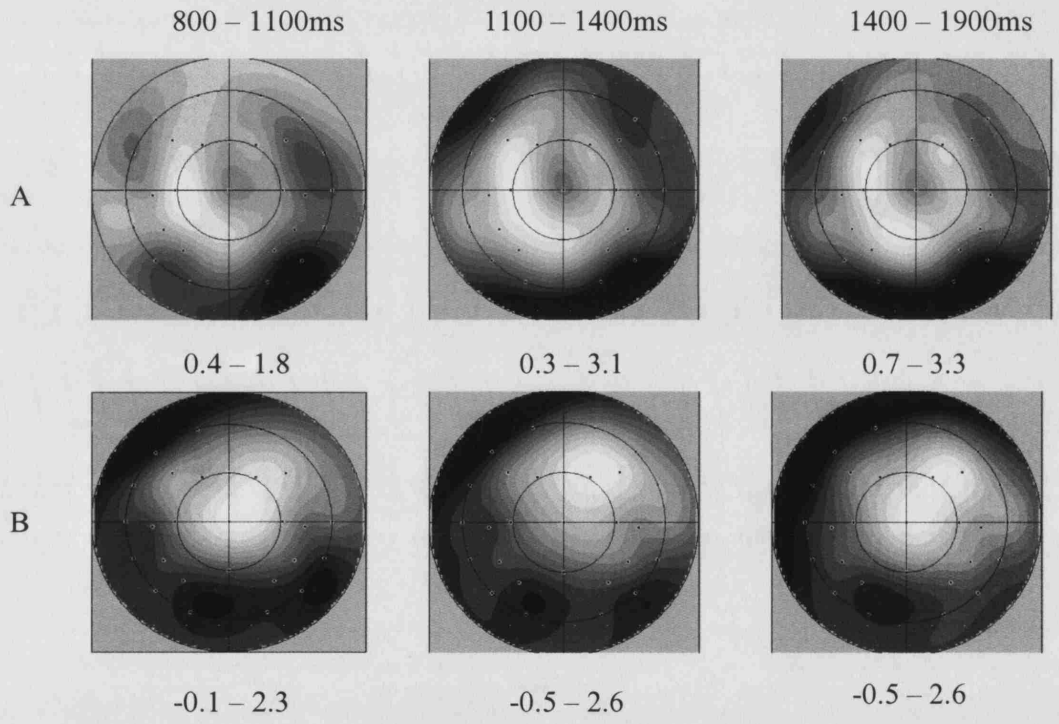

Figure 6.5 Spherical spline maps showing scalp distributions of the emotion effects associated with recognised items attracting correct (A) and incorrect (B) source judgments in the latency regions shown. Each map is proportionately scaled between the extremes of the depicted effect (values in μV given below in each case).

Additional Analyses Across Experiments

While the late-onset effects of emotion were large and robust in both the present experiment and in those described in chapter 4, the early (300–500 msec) effects were small in amplitude and only weakly significant.

To characterize these effects further, the data from the 300- to 500-msec latency region were analyzed across both this experiment, and experiment one described in chapter 4. We performed an ANOVA employing factors of experiment, item type, hemisphere, AP position, and lateral site on the data from the same 18 lateral electrode sites used previously. This revealed a significant interaction among item type, hemisphere, AP position, and lateral site, $F(2.3,78.3) = 4.37$, $p < .05$.

A subsidiary ANOVA was conducted on the four electrode sites where the effects appeared largest (the anterior and posterior lateral temporal sites of each hemisphere), revealing a main effect of item type, $F(1,34) = 13.6$, $p = .001$.

Importantly, none of these effects showed interactions with experiment, indicating a small but reliable effect of emotion at these sites across the two experiments.

The waveforms from the right posterior lateral temporal site, at which the effect is clearest, are shown in Figure 6.6, collapsed across the two experiments. Figure 6.6 also illustrates that the onset of emotion effects precedes the left parietal old/new effect.

Discussion

Behavioural Data

As had been observed in the previous experiments, items encoded in positive contexts were recognised at a slightly, but significantly, higher level of accuracy than their

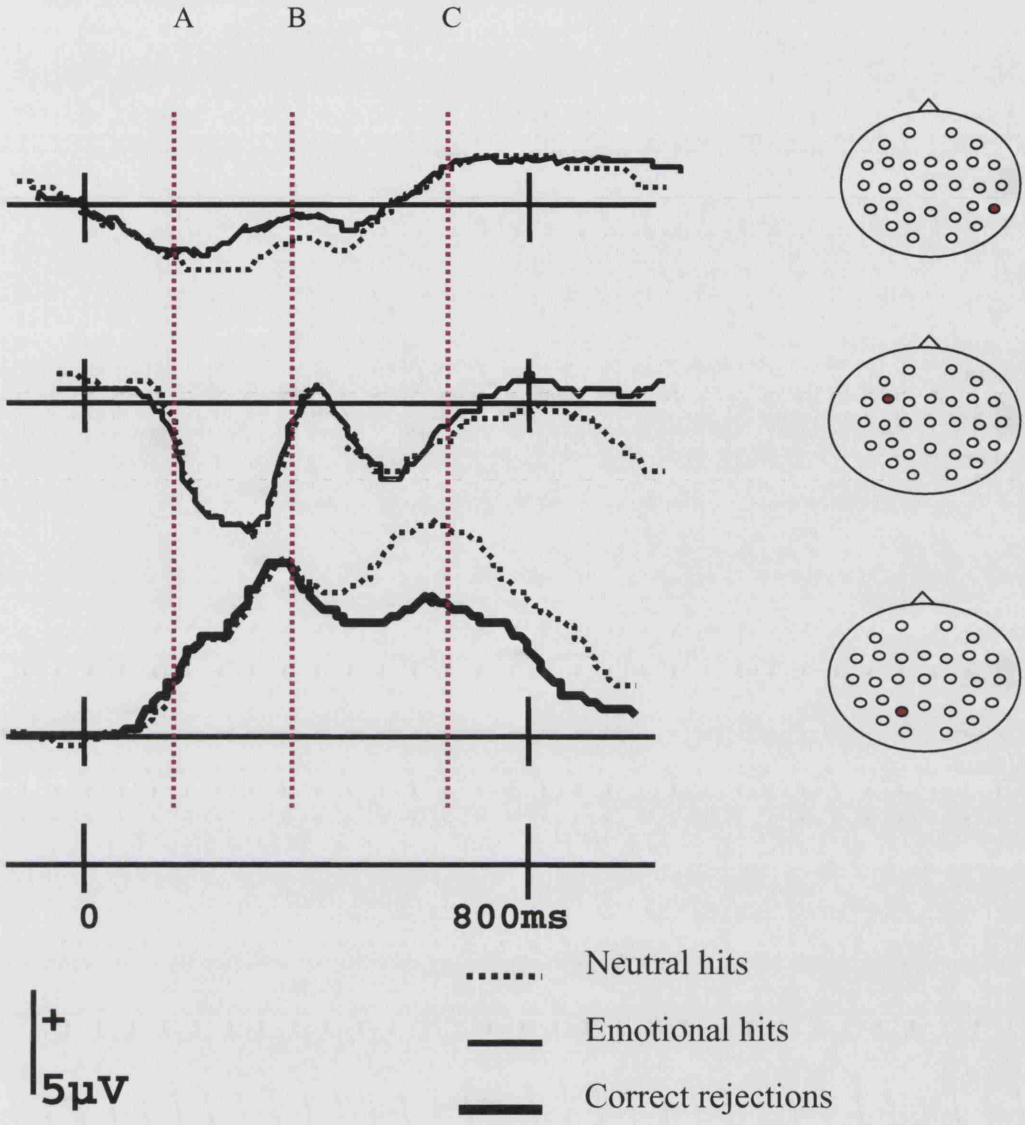

Figure 6.6 ERP waveforms from the sites depicted showing relative onset timing of early emotion effects (A), episodic retrieval (B) and late emotion effects (C).

negative and neutral counterparts. This replication suggests that, in our paradigm, association of a neutral cue with a positively valenced context leads to small but fairly robust improvements in recognition memory. Furthermore, the extent of this

recognition advantage is correlated with how positive individual subjects rate the context to be.

Both positive and negative contexts were associated with a significantly increased proportion of hits attracting accurate source judgements. The inclusion of a 'don't know' option in our source memory task means that the figures obtained are fairly accurate estimates of veridical source memory. It should also be noted that our ERP waveforms for source hit trials will contain far fewer trials reflecting 'lucky guesses' than would be the case in a 3-way forced choice design and therefore accurately represent differences between successful and unsuccessful contextual recollection. Source memory correlated significantly with distance from zero of individual subjective valence scores (i.e. absolute valence), suggesting that the ability of an emotional stimulus to manipulate memory may depend on the strength of emotion elicited by that stimulus. These effects were confirmed as being independently significant for both positive and negative contexts. The possibility that these findings merely reflect response bias in favor of the ''emotional'' sources can be discounted on two grounds. As shown in Table 6.1, the overriding majority of false alarm trials (when subjects misclassified new pictures as old) were given a ''don't know'' response, rather than an emotional source endorsement. Furthermore, the majority of source errors for correctly recognized neutral items were also in the ''don't know'' category rather than in the form of a source misattribution. Together, these findings suggest strongly that the greater accuracy for emotional versus neutral source judgments cannot be explained by a bias in favor of the emotional response categories

The findings of enhanced memory for the pre-experimentally neutral items encoded in emotionally valenced vs. neutral contexts is consistent with the literature regarding both free recall and recognition (Phelps et al, 1997; Hamann et al, 1999; Erk et al,

2003; see chapter 1), although other studies have shown enhancements in recognition memory to be inconsistent (Maratos et al, 2001; Danion et al, 1995). Once again we found a dissociation in the effects of positive and negative on recognition performance, but also between negative context effects on item and source memory. These findings were not predicted a priori and do not correlate simply with valence or arousal differences.

We have discussed evidence for a dual-process framework underlying recognition performance (see chapter 1). It may be that emotional modulation consists of multiple components, with an arousal component perhaps acting solely or primarily by increasing the number of stimuli 'recollected' whilst there are valence specific effects on either both components or on 'familiarity' alone. These valence specific differences may reflect different neurochemical mediation of positive and negative emotion processing (see chapter 5 discussion).

An alternative explanation may be suggested by the finding that in the negative condition extremely unpleasant backgrounds were associated with poorer item memory (though an increased proportion of recollection) than moderately unpleasant contexts. It may be that while there is a general enhancement of memory for items encoded in emotional contexts, when these are particularly attention-grabbing they may draw attention from the critical stimuli, and thus impair encoding. The predicted pattern of memory enhancement with moderately emotional stimuli, with impairment associated from extreme arousal, is consistent with the pattern of results seen in the present experiment. However, attempts to fit recognition performance against either valence or arousal for negative stimuli provided no statistical evidence for the inverted-U shape predicted by this account, possibly due to inter-subject variability and a relatively coarse rating scale.

ERP data

The ERP old/new effects reflected both memory effects common to test items encoded in either neutral or emotional contexts and, later, differential effects of emotional context. All classes of old item elicited a left parietal positivity relative to correctly rejected new items, and this 'left parietal effect' was considerably larger for items attracting correct source judgements, in accordance with the views of various authors who have proposed it to be an electrophysiological correlate of recollection (Smith, 1993; Rugg et al, 1996; Düzel et al, 1997; Wilding, 2000). This left parietal effect was not modulated by emotion in this experiment, implying that during retrieval processing any effect of emotion is not on the initial recovery of stored information. However, it should be noted that some authors have suggested that retrieval of item and source information may occur in temporally distinct stages (e.g. Senkfor and Van Pettern, 1998). If this is the case then it is possible that contextual retrieval processing *per se* is modulated by emotion. However, unlike the effects observed in the present experiment, the effects proposed by Senkfor and Van Petten (1998) to reflect memory search for source information were not modulated by accuracy of source memory.

As in our earlier ERP experiments, the waveforms associated with items encoded in emotional vs. neutral contexts dissociated strongly around 800ms after stimulus presentation. This suggests that emotional aspects of a memory trace modulate its post-retrieval processing, whether or not that emotional information is task relevant. Furthermore, ERP modulations can occur even without successful retrieval of source memory, meaning that emotional influences at encoding may result in changes at retrieval without conscious awareness.

It is worth noting that although across experiments the effects of emotion on waveform amplitude occur at similar times after stimulus presentation, in the present experiment topographic dissociation of neutral and emotional memory effects occurred later. One possibility is that this difference arises from the task-relevance of retrieved neutral information in the present experiment, and that some of the effects seen when source information is task-irrelevant are due to obligatory engagement of processes by emotional material which may be engaged by neutral material when necessary. If this is the case, as the difference between emotional and neutral hits seen between 800-1100ms post-stimulus shows topography not previously reported in source experiments utilising emotionally neutral material, we propose that it might represent a correlate of assessing the emotional relevance of a stimulus. As this was not task-relevant in earlier experiments, such processing was elicited only by emotional stimuli, which did so automatically. In the present experiment, the emotional significance of all contexts was task relevant, and therefore retrieval of emotional and neutral memories could elicit similar activity.

In any case, subsequently the topographies of old/new effects for emotional and neutral material did differ reliably, implying emotion-specific retrieval processing. This is consistent with the work described in the previous experiments, and with the findings of some others (Dolan et al, 2000; Maratos et al, 2001) discussed in chapter 2. As was discussed in chapter 4, these late-onsetting effects are similar to a 'late positive potential' which has previously been reported to differentiate emotional and neutral pictures from the IAPS set (Dolcos & Cabeza, 2002; Keil et al., 2002; Cuthbert et al., 2000; Schupp et al., 2000; Palomba et al., 1997; Mini et al., 1996). Thus, a parsimonious explanation for the effects observed in the present experiment is that similar processes are engaged by emotionally valenced perceptual representations

whether they are sensory or mnemonic in origin. Small differences in distribution and latency may reflect direct versus indirect conveyance of the emotional information in these scenarios.

The major difference between emotional and neutral source misses was that items encoded under emotional conditions elicited significant right frontal positivity. This right frontal effect has previously been proposed to be a correlate of post-retrieval processing (see Rugg and Allan, 2000; chapter 1) and may be related to activations seen in right dorsolateral prefrontal cortex in fMRI studies of recognition memory (e.g. Henson et al, 2000), and modulated by emotional context (Maratos et al, 2001). The right frontal effect was also modulated by correct vs. incorrect source memory judgements. One possibility is that post-retrieval processing of memory is sensitive to salience of available information – right frontal effects are more commonly seen when there are increased task demands, such as in source memory vs. simple recognition tasks, such that any retrieved information affecting a task-relevant judgement must be processed. Emotional memories are inherently salient because of their association with reward or punishment. It is possible that the salience of emotional memories may be processed without conscious awareness of the emotional associations of the cue, and thus enhance renewed attempts to retrieve enough information for the source judgement. Another possibility is that enough information is retrieved in some trials for the subject to be aware that the memory is emotional, but not to discriminate positive and negative. This being the case, there might be more source miss trials associated with partial recollection of emotional than neutral contexts (as the partial recollection that a context was emotional is insufficient for the task, whereas remembering that it was not emotional is sufficient) and hence more cases where post-retrieval processing could have occurred. However, that is unlikely to have been a

major contributory factor to the effects observed, given the equivalent left parietal effects for emotional and neutral source misses.

The topographies of emotion effects for source hits and misses differed significantly, suggesting that the effects of emotion in the present experiment are not carried solely at an unconscious level, and cannot be accounted for solely on the basis of effects at encoding. The difference between emotional and neutral source hits, was widespread across the scalp, but with a principally left-sided focus. This is consistent with the findings of some authors of left lateralisation of emotion related activity for consciously vs. unconsciously processed emotional stimuli (Morris et al, 1998) or semantic monitoring of emotional information (Crosson et al, 2002). In contrast, the more restricted effect of emotion on source misses was right lateralised, reflecting principally the modulation of the right frontal effect, though differences were also seen over right central scalp.

Summary

The present findings, together with those presented in chapter 4, indicate that regardless of task relevance, emotional manipulation of the context within which a stimulus is encoded can result in changes in both behavioural and electrophysiological measures of retrieval. Changes in the neural and cognitive processing of a stimulus due to emotional context are modified by, but do not depend upon, explicit recollection of that context.

The emotion effects we have observed are topographically dissociable from those correlated with recognition memory processing for otherwise identical material encoded in neutral contexts, implying that retrieval or post-retrieval processing of

emotional memory recruits additional neural structures and cognitive processes. The timing of our ERP effects suggest that the primary influence of emotion on retrieval may be on post-retrieval processes, both in the context of emotion specific processing which might relate to re-experience of or reaction to emotions elicited during exposure to emotional material at encoding and modulation of 'monitoring' processes which may also be engaged for emotionally neutral information. Additionally emotion may modulate initial cue processing of items associated with emotional contexts, and whether information about such contexts is successfully retrieved influences the subsequent pattern of emotional modulation. The next experiment aims to reinforce these findings, and to examine the different neural structures modulated by emotion following successful or unsuccessful source retrieval.

Chapter 7: fMRI Correlates of the Intentional Retrieval of Emotional Context

Introduction

In the previous chapters, distinct patterns of neural activity have been identified which appear to reflect retrieval processing for emotional and non-emotional memories. The findings imply that memory for items with an emotional study history elicits activity in structures associated with processing of emotional stimuli, in addition to modulating those typically engaged during memory retrieval. However, such effects may be accounted for by 2 alternative mechanisms. Firstly, stimuli presented in emotional contexts may, by virtue of association, themselves acquire emotional value and subsequently elicit activity in emotion-processing structures without the necessity to retrieve information about the context. Secondly, recognition of the item may be associated with recollection of the encoding episode, including the emotional context, which subsequently engages emotional processing.

The ERP findings in chapter 6 indicate that qualitatively different cognitive processes engaged during memory retrieval can be modulated by emotion, some of which may not require explicit awareness (as operationalised by source judgements) of the emotional nature of an item's encoding context.

Awareness of emotional stimuli or contingencies has previously been shown to modulate processing in emotion-sensitive structures. For example, masked presentation of fear-conditioned faces elicited responses in right amygdala alone, whilst unmasked presentation resulted in left amygdala responses (Morris et al, 1998a). Similarly, Gläscher and Adolphs (2003) have reported differential effects of

left and right amygdala lesions on skin conductance responses (SCR) to masked and unmasked emotional pictures. Another interesting finding is that in classical conditioning, which is not dependent upon explicit awareness of contingencies between conditioned and unconditioned stimuli, awareness of these contingencies is associated with enhanced activity in the insula and middle temporal gyrus (Critchley et al, 2001).

In the present experiment, pre-experimentally neutral pictorial stimuli were associated with positive, negative and neutral backgrounds at study and differential neural activity elicited by these stimuli during a source memory task investigated. The focus was on the interaction between emotion effects and the accuracy of source judgements, with the hypothesis that modulatory effects of emotion on source miss trials would likely be consequences of modified item value, in the absence of explicit retrieval of emotional context, while source hit trials would reflect retrieval of item-source associations. It was hypothesised that some of the emotion effects reported the earlier fMRI experiment (chapter 5), specifically those in left amygdala and insula, would be dependent upon explicit retrieval of emotional contexts whilst others would reflect processing resulting from modification of the value of retrieval cues.

Methods

Subjects

Nineteen right handed young adults (age range 18-30 years, mean 21) were employed as subjects and remunerated at £7.50/hour. All were in good health with no history of neurological or psychiatric illness. One subject was excluded from the final analysis due to excessive movement-related artifacts. Of the remaining 18 subjects, 8 were

female. The experiment was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Stimulus Materials and List Construction

Stimulus materials and lists were identical to those used in previous experiments (see chapter 3b) and will not be repeated here.

Study Procedure

In the study phase, stimuli were presented via a mirror mounted on the head coil of the fMRI scanner, in direct view of the supine participant, at a distance of approximately 50cm from the projection screen. The background was initially presented alone on the screen for 3s. During this time subjects indicated whether they judged the backgrounds to be pleasant, unpleasant or neutral, using a keypad in the right hand to assign them to these 3 categories. 3s after presentation of the context, the critical object was superimposed centrally upon the background, and subjects were required to imagine a connection between background and object. This connection was made covertly. The object and background were presented together for 4.5s, and the screen was then blanked for 750ms before presentation of the next background. Six practice trials were given prior to the study proper, during which the subjects were required to describe verbally the connections they had made between background and object, thereby ensuring they understood the task. During the study phase proper, a rest break was given after 92 trials, the first two trials of each of the subphases being neutral filler items.

Test Procedure

The test phase followed the study phase after a delay of five minutes, during which a serial subtraction task was performed to prevent rehearsal. Stimulus delivery used the same setup as during study. A white asterisk was presented against a black background for 500ms, following which the test item was presented for 1000ms. This was followed by a white fixation cross on a black background for approximately 2300ms before presentation of the asterisk denoted the imminent onset of a new trial. This sequence of events gave a stimulus onset asynchrony (SOA) of 3.8s. 120 'null events', consisting of the white fixation cross for an additional 1.5s in place of the white asterisk and test item, were incorporated into the test list, allowing estimation of baseline. Subjects were instructed to respond, as quickly and accurately as possible, with one of five buttons: one indicated that the object was being seen for the first time (new), another that the subject knew the object was old but could not remember the background with which it had been paired at study, with the remaining three buttons indicated that it was a remembered object from a neutral, negative or positive background. This approach is a hybrid of those adopted in Remember/Know (R/K) and source memory experiments, and allows both validation of the accuracy of confident responses and minimizes guessing. It is similar to that employed in the experiment described in chapter 6, but combines recognition and source discrimination into a single judgment. For the purposes of analysis, trials which received a 'don't know' judgement or which received an incorrect source attribution were collapsed into a single 'source miss' category.

The test list was split into 2 equal parts, with the first two stimuli of each subphase being filler items. Prior to the test phase proper an example test phase was given, containing the 6 items from the practice study list, plus 3 new items. None of these

items appeared in the subsequent test list. After the test phase, subjects were debriefed and questioned about perceived performance and strategies used in the task.

Imaging and Image Processing

MRI data were acquired from a 1.5T Siemens SONATA system (Siemens, Erlangen, Germany) equipped with a head coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD (blood oxygenation level dependent) contrast, with a repetition time (TR) = 2.7s, giving an effective sampling rate of approximately 2Hz at both study and test. A combination of slice-tilting and z-shimming were used to minimize signal loss and distortion in basal temporal and frontal areas (Deichmann et al, 2003). 35 slices of 2.5mm thickness were acquired, with an inter-slice gap of 1.3mm, giving whole brain coverage, with the exception of the vertex. Data were acquired during four separate sessions (two each at study and test) with the first five volumes of each session discarded to allow for T1 equilibration effects. Images were realigned, slice-time corrected, normalised to a standard echo-planar image template and smoothed with a Gaussian kernel with full-width half maximum of 8mm.

Statistical Analysis of Images

Data were analysed using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, UK; Friston et al, 1995a) using a random-effects analysis. Test data were modeled as 12 discrete event types: old items from each of the 3 categories of old items (neutral, negative, positive) were separated according to whether they received correct source judgments (source hits), received either 'old, but source unknown' or incorrect source judgments (source misses) or

were incorrectly judged to be new (misses); new items were separated into those which were correctly rejected as new (correct rejections), or incorrectly judged to be old (false alarms). Categorisation into valences was based on the ratings of individual subjects. A separate regressor of no interest was formed from the two filler items at the start of each list, and those trials where no response was logged. Principal contrasts were between those events which received correct responses (i.e. source hits, source misses and correct rejections).

Regressors modeling events were convolved with a standard canonical haemodynamic response function, with movement parameters modeled as potentially confounding covariates. Linear contrasts of parameter estimates were estimated for each subject, and initial statistical parametric maps were generated. For some contrasts, positive and negative hits were collapsed to form individual 'emotional source hit' and 'emotional source miss' conditions, analogous to our previous ERP studies (Smith et al, 2004; chapters 4, 6). Principle contrasts were all based on one-tailed t-tests with a significance level of $p<0.001$ (uncorrected) and a spatial extent threshold of at least 5 contiguous voxels ($k=5$). Some regions which were predicted *a priori* were not revealed when the spatial threshold was employed, and are reported as tentative findings. In a number of cases we utilised 'inclusive masking' to reveal voxels common to two or more contrasts.

Results

Behaviour

Recognition accuracy and associated reaction times (RTs) are shown in table 7.1, together with accuracy for source judgements to old items. ANOVA of hit rates

showed a main effect of condition [$F(1.9, 30.3) = 25.5$; $p < 0.001$; degrees of freedom corrected using the Greenhouse-Geisser method]. Subsidiary ANOVAs revealed that items encoded in positively valenced contexts were more likely to be recognised than items encoded in neutrally [$F(1,17) = 65.3$; $p < 0.001$] or negatively [$F(1,17) = 12.5$; $p < 0.005$] valenced contexts, whilst items encoded in negative contexts were more

Table 7.1 Mean accuracies and reaction times (Standard deviations in parentheses)

	Neutral	Negative	Positive	Correct Rejection
Hit accuracy	0.80 (0.08)	0.84 (0.08)	0.89 (0.06)	0.92 (0.05)
Source accuracy	0.44 (0.16)	0.59 (0.16)	0.56 (0.17)	-
RT (msec)	964 (312)	977 (399)	953 (277)	1069 (293)

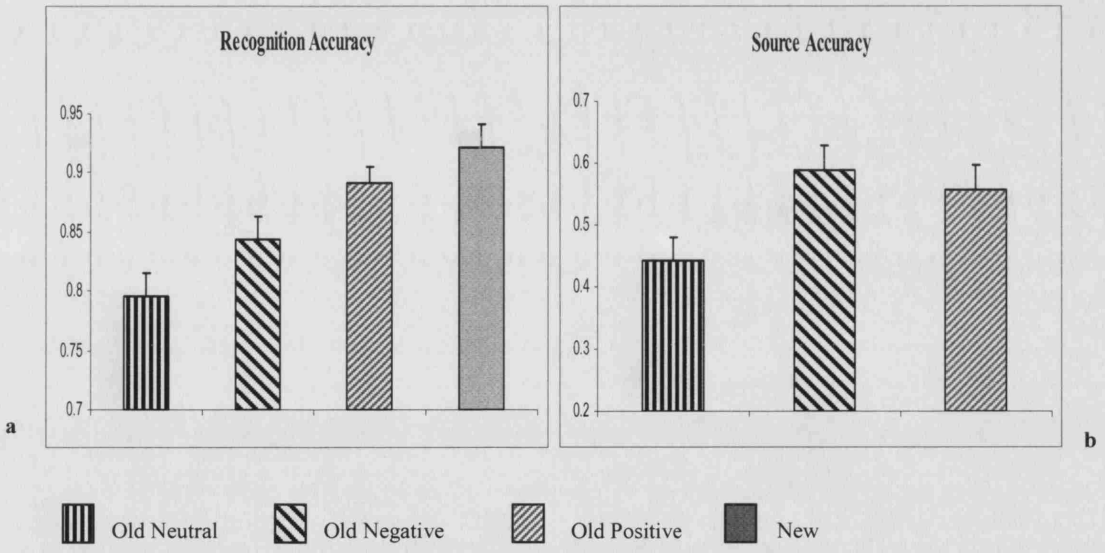

Fig. 7.1 Histograms showing accuracy of recognition judgments (a) and the proportion of recognised items attracting correct source judgments (b).

likely to be recognised than those from neutral backgrounds [$F(1,17) = 10.7$; $p < 0.01$] (fig 7.1a). Items encoded with neutral backgrounds were less likely to receive an accurate source judgement than those encoded with either negative [$F(1,17) = 12.2$; $p < 0.005$] or positive [$F(1,17) = 10.4$, $p < 0.01$] backgrounds (fig 7.1b). There was no significant difference between source accuracy for positive and negative contexts [$F(1,17) < 1$], and no significant differences in RTs to hits.

fMRI data

The principal contrasts of interest were i) common effects for the three source hit conditions (neutral, negative and positive) vs. correct rejections (old/new effects), ii) between a collapsed emotional 'source hit' (old item with correctly attributed source) condition (weighted combination of positive and negative hits) and neutral source hits (emotional source hit effects), iii) between emotional and neutral source misses (recognised old items attracting either source misattributions or 'old, source unknown' judgments) (emotional source miss effects) and iv) the interaction between emotion and source accuracy, reflected in differences in emotion effects for source hits and misses. The mean number of trials (range in parentheses) contributing to each of the critical conditions were: neutral source hits, 22 (16-38); neutral source misses, 26 (16-36); negative source hits, 30 (18-41); negative source misses, 20 (16-30); positive source hits, 32 (20-40); positive source misses, 22 (16-33); correct rejections, 75 (50-87).

Retrieval effects

An *inclusive* mask incorporating the outcomes of contrasts between source hits and

correct rejections from neutral, negative and positive conditions revealed activity common to successful retrieval of emotional and neutral source memories (table 7.2). Significant effects were elicited in left lateral parietal and posterior cingulate cortex, precuneus, inferior temporal lobe and bilateral prefrontal cortex, corresponding to those reported in other event-related fMRI studies of source memory (Henson et al, 1999; Rugg et al, 2002). Effects were also seen in left anterior insula and the basal ganglia. Memory effects for source miss trials were much more restricted, being present in left cuneus and left prefrontal cortex.

Region			Peak Coordinates				
			Voxels	x	y	z	Peak Z
L	Precuneus	(BA 7)	8	-6	-72	45	4.19
L	Cuneus	(BA 7)	73	-3	-66	33	4.22
R	Precuneus	(BA 31)	11	18	-60	27	3.93
L	Angular gyrus	(BA 39)	5	-45	-66	33	3.52
L	Sup. parietal lobe	(BA 7)	51	-27	-63	48	4.57
L	Post. Cingulate	(BA 30)	10	-6	-57	9	3.76
L	Inf. Temporal lobe	(BA 37)	13	-54	-42	-15	4.3
R	Lat. Globus Pallidus		12	15	3	-3	3.41
R	Caudate body		5	12	6	12	3.86
L	Putamen		6	-12	12	-3	3.38
L	Insula	(BA 13)	15	-36	21	3	4.27
R	Inf. Frontal gyrus	(BA 45)	5	33	24	3	3.92
L	Inf. Frontal gyrus	(BA 46)	59	-51	45	0	4.56
L	Sup. Frontal gyrus	(BA 8)	16	-3	33	45	5.18
L	Mid. Frontal gyrus	(BA 46)	74	-48	33	24	5.06
		(BA 10)	5	-36	57	9	3.9

Table 7.2 Common source hit effects (inclusive mask of neutral, negative and positive source hits – correct rejections). Brodmann areas are approximations based on peak coordinates.

Emotion Effects – Source Hits

Direct comparison of negative and positive source hits revealed that the former were associated with greater activity in left cerebellum, right fusiform gyrus and right posterior parietal cortex, whilst positive hits showed greater activity in medulla oblongata.

However, these effects were much more restricted than those revealed by contrasts with neutral items so all subsequent analyses collapsed positive and negative into a single emotional condition to improve statistical power.

Region			Peak coordinates				
			Voxels	x	y	z	Peak Z
R	Cerebellum		14	24	-33	-21	3.99
L	Parahippocampal gyrus	(BA 36)	6	-36	-24	-18	3.32
L	Sup. Temporal lobe	(BA 22)	6	-48	-15	-6	3.11
		(BA 38)	10	-45	0	-10	3.65
L	Amygdala		8	-27	-6	-15	3.24
L	Parahpc/Inf. Frontal gyri	(BA 34/47)	99	-12	-6	-15	5.37
L	Anterior Insula	(BA 13)	5	-42	-3	-6	4.56
R	Subcallosal cingulate	(BA 25)	5	3	18	-12	3.93
L	Subcallosal cingulate	(BA 25)	5	-6	21	-12	3.4
L	Inf. Frontal gyrus	(BA 47)	18	-33	18	-9	3.31
R	Inf. Frontal gyrus	(BA 47)	5	33	27	-6	4.27
L/R	Anterior cingulate	(BA 24)	10	0	24	-6	3.73
R	Anterior cingulate	(BA 32/24)	8	3	39	3	4.03
L	Mid. Frontal gyrus	(BA 11)	5	-30	39	-12	4.21
L	Med. Orbitofrontal cortex	(BA 11)	5	-3	39	-21	3.62
L	Sup. Frontal gyrus	(BA 9)	8	-6	57	36	3.61
L	Med.Frontal gyrus	(BA 10)	24	-3	66	6	3.98

Table 7.3 Effects revealed in the contrast of emotional and neutral source hits

Contrasts between emotional and neutral source hits revealed (table 7.3) that retrieval of emotional contexts was associated with increased activity in left amygdala. In addition there was enhanced activity in left parahippocampal gyrus and anterior insula, the brainstem, bilateral anterior cingulate cortex (ACC) subgenual cingulate, and bilateral prefrontal areas, especially left VMPFC.

Region				Peak coordinates			
			Voxels	x	y	z	Peak Z
R	Precuneus	(BA 19)	18	18	-78	39	3.95
L	Cuneus	(BA 18)	30	-6	-75	15	4.53
R	Mid. Occipital gyrus	(BA 19)	8	51	-57	-3	3.77
R	Lingual gyrus	(BA 18)	53	15	-57	3	4.47
L	Fusiform	(BA 37)	15	-48	-57	-15	3.63
		(BA 20)	20	-42	-9	-24	4.05
R	Fusiform	(BA 20)	5	42	-15	-24	4.18
R	Mid. Temporal gyrus	(BA 21)	12	60	-54	6	3.56
R	Inf. Parietal lobule	(BA 40)	38	48	-36	42	4.61
R	Lat. Globus pallidus		13	21	-9	6	3.71
R	Amygdala		20	27	-3	-18	3.89
R	Sup. Temporal gyrus	(BA 38)	14	51	15	-18	3.82
L	Sup. Temporal gyrus	(BA 38)	14	-48	12	-21	3.48
L	Mid. Frontal gyrus	(BA 9)	11	-48	9	36	3.84
R	Mid. Frontal gyrus	(BA 11)	5	33	36	-12	3.78
R	Inf. Frontal gyrus	(BA 45)	5	63	12	21	4.03
L	Inf. Frontal gyrus	(BA 47)	6	-57	21	0	3.37
R	Sup. Frontal gyrus	(BA 10)	22	33	54	-3	3.96
L	Sup. Frontal gyrus	(BA 9)	9	-12	54	36	4.3

Table 7.4 Effects revealed in the contrast of emotional and neutral source misses

Region			Voxels	Peak coordinates x	y	z	Peak Z
Source Hits (Emotional – Neutral) > Source Misses (Emotional – Neutral)							
L	Sup. Temporal gyrus	(BA 22)	5	-48	-18	-6	3.79
L/R	Mid-cingulate gyrus	(BA 23)	5	0	-12	27	3.25
L	Midbrain		30	-3	-12	-15	5.02
L	Amygdala		7	-21	0	-18	3.46
L	Mid. Frontal gyrus	(BA 11)	5	-27	42	-12	3.97
L	Insula	(BA 13)	2*	-42	-3	-6	3.19
L	Med. Frontal gyrus	(BA 10)	4*	-6	63	6	3.38
Source Misses (Emotional – Neutral) > Source Hits (Emotional – Neutral)							
R	Cuneus	(BA 18)	12	6	-75	18	4.3
R	Lingual gyrus	(BA 18)	5	15	-78	-9	3.27
R	Inf. Temporal gyrus	(BA 20)	6	57	-36	-15	3.25
L	Trans. Temp. gyrus	(BA 41)	5	-33	-27	9	3.2
R	Lat. Globus pallidus		6	21	-6	3	3.4
R	Parahip/Amygdala		24	30	3	-15	3.46
R	Sup. Frontal Gyrus	(BA 10)	20	42	51	-6	3.45

Table 7.5 Regions showing an interaction between emotion and source memory. Regions marked with an asterisk did not survive the spatial extent threshold, and should be regarded as tentative findings.

Emotion Effects – Source Misses

Differences in activity elicited by emotional and neutral source misses are reported in table 7.4. This contrast reflects differences in neural activity arising from emotional study history in the absence of accurate recollection of that history. We observed enhanced activity for items encoded in an emotional context, compared to neutral items, in right amygdala. Differences were also evident in right occipital cortex,

precuneus and lingual gyrus, bilateral fusiform areas, right inferior parietal lobule and bilateral prefrontal areas, particularly right superior frontal gyrus.

Interaction of Source Memory and Emotion

It was next examined whether there was differential emotional activity during retrieval for source hit compared to source miss trials. In effect such a contrast reflects modulation as a function of successful episodic retrieval of emotional context (table 7.5). Source hit trials were associated with greater emotional responses in left amygdala (fig 7.2). Enhanced activity was also seen in midbrain, left superior temporal gyrus, bilateral mid-cingulate cortex and left orbitofrontal cortex (fig. 7.3). It was predicted *a priori* that anterior insula and VMPFC would be involved in retrieval of emotional context, so it was then investigated whether these areas showed any response by removing the spatial extent threshold. This revealed that small regions of left anterior insula and left VMPFC were significantly more active in contrasts of emotional and neutral source hits than source misses, though this should be regarded as tentative given the reduced threshold. The reverse contrast revealed greater emotion-related modulations of right amygdala activity for source miss than source hit trials (fig 7.2). Additional effects were evident in right parahippocampal cortex, cuneus, bilateral temporal gyri and right prefrontal cortex (fig 7.3). The regions of left and right amygdala revealed in these contrasts, together with associated signal changes are shown in figure 7.2. In order to elucidate the apparent laterality of amygdala effects in source hit and source miss conditions, contrast estimates from left and right amygdala in each subject were contrasted. The voxels were selected using the peak coordinates from the interaction reported above, and were confirmed as lying within the amygdala of each subject

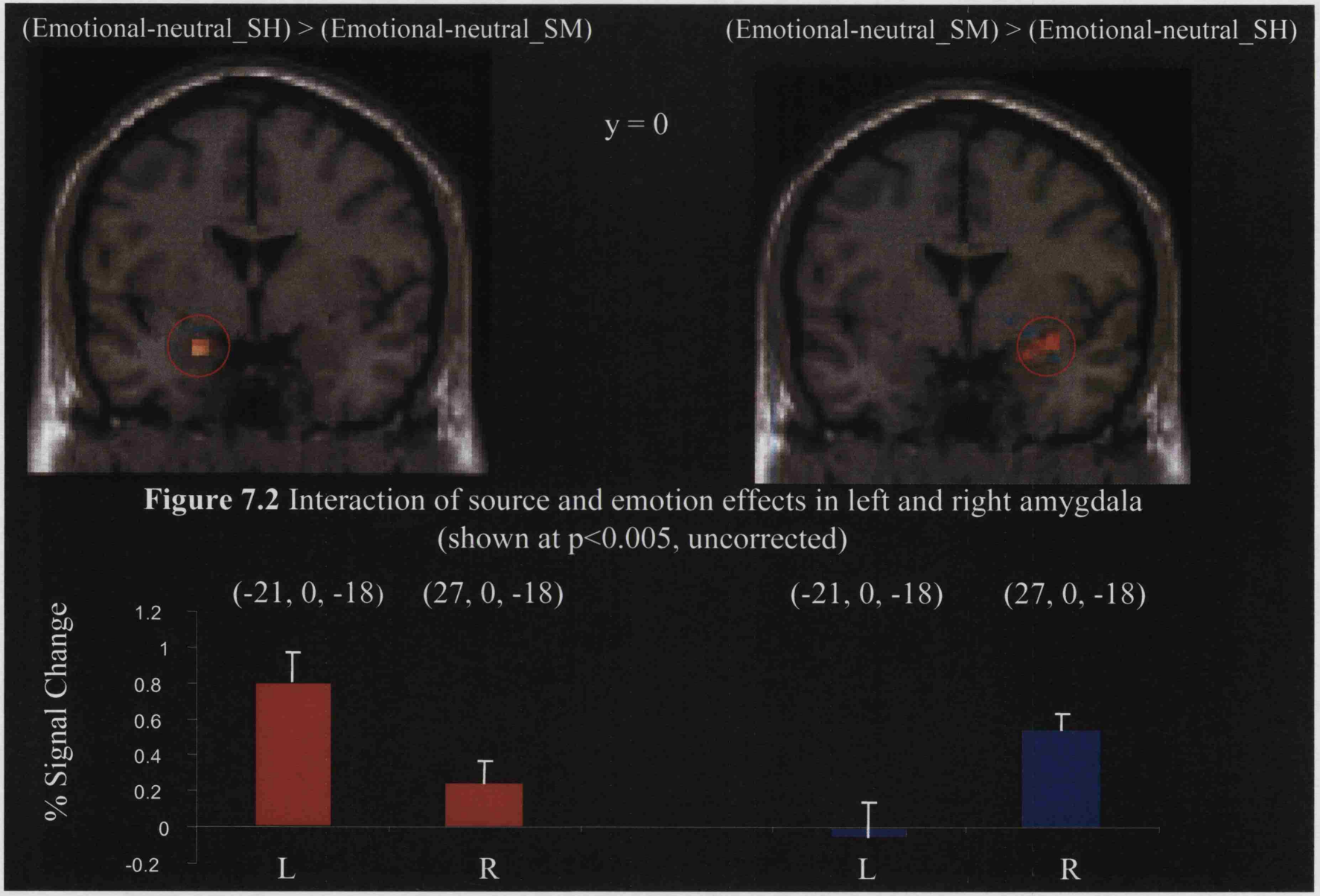

Figure 7.2 Interaction of source and emotion effects in left and right amygdala (shown at $p<0.005$, uncorrected)

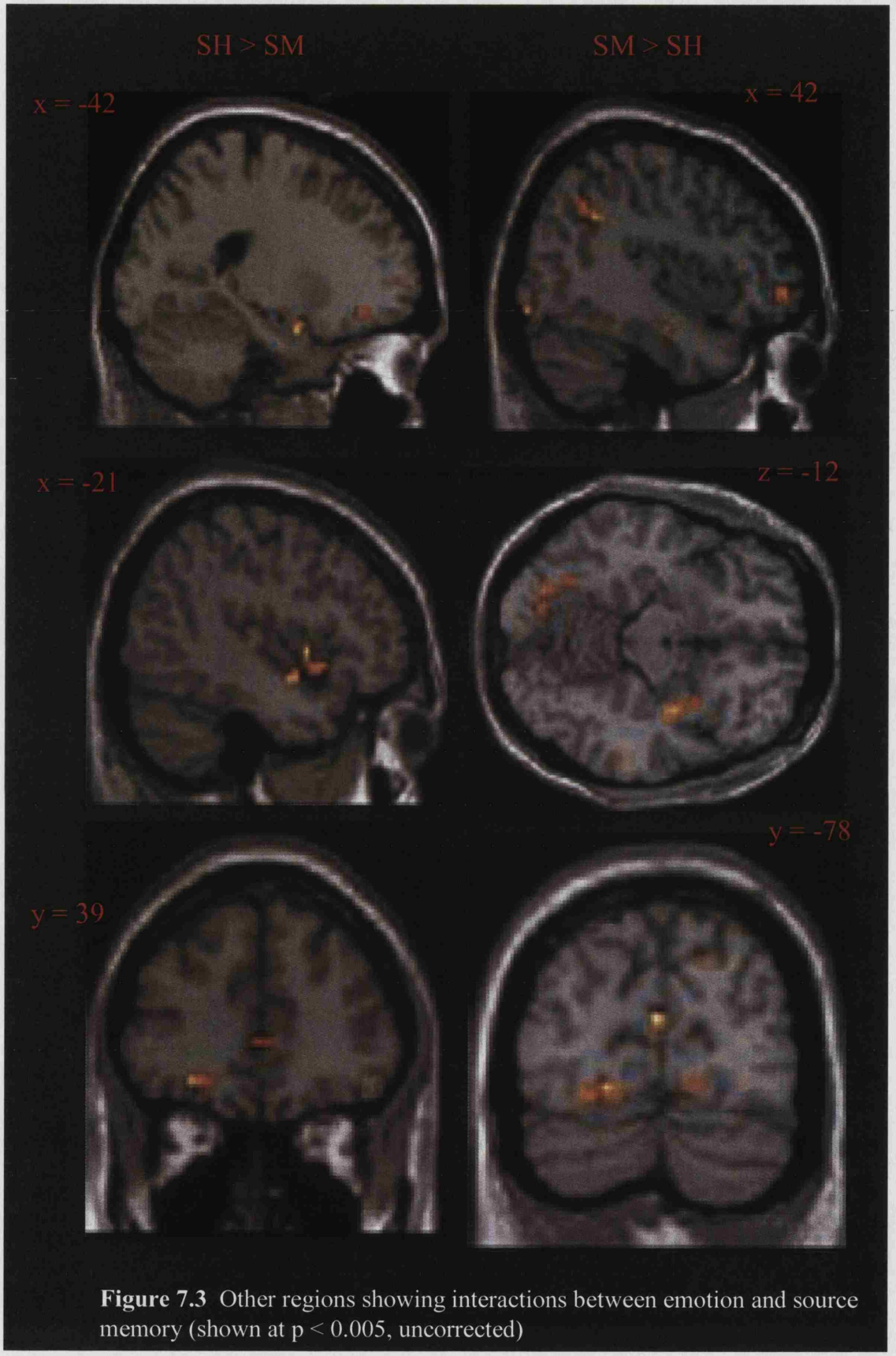

Figure 7.3 Other regions showing interactions between emotion and source memory (shown at $p < 0.005$, uncorrected)

on the basis of the structural images. Repeated measures ANOVA on these contrast estimates revealed a significant hemisphere by condition interaction [$F(1,17) = 27.13$, $p < 0.001$]. Although choosing voxels based on the contrast between emotion effects on source hits and misses results in a partially biased measure, this test provides additional support for the lateralisation of amygdala responses during retrieval of emotional memories according to the specificity of emotional information retrieved.

Discussion

Behaviour

The modulation of memory processing by emotion is reflected in differential neural activity during retrieval of memories formed in association with emotional contexts, and improved memory for these events. Here we describe evidence for engagement of distinct circuits during retrieval of emotional memories, demonstrating dissociable effects of emotion on the neural correlates of retrieval processing according to whether or not there is accurate recollection of the encoding context.

The behavioural findings of enhanced memory following emotional manipulation are consistent with previous work described in this thesis and elsewhere (see chapter 5; see also Christianson, 1992). In particular, the dissociation between effects of positive and negative contexts on item and source memory has been reported earlier. This dissociation may reflect distraction by the more 'attention-grabbing' negative images away from associated neutral objects (impairing recognition, but not affecting the conditionalised probability of accurate source judgements) and/or different neuromodulatory effects of positive and negative emotion on memory (see Erk et al, 2003; Smith et al, 2004a; chapter 2). It is worth noting that accurate source

judgements could be made either due to recollection of the actual context associated with each object, the context-object association formed by the subject or an awareness of the prior emotional association without explicit recollection of the context itself. During post-scanning debriefing all subjects indicated that the great majority of source judgements followed recollection of the context and association, but it cannot be discounted that some source hit trials may have been accompanied by awareness of the valence paired with an object in the absence of full contextual recollection.

fMRI Data

One of the most notable findings was the lateralisation of amygdala responses to items encoded in emotional contexts, according to whether sufficient information was retrieved to support source memory judgements. The possible roles of the amygdala in emotional retrieval were discussed in chapter 5, in relation to the left amygdala activation reported there, and other findings both in humans and animal models. The present findings suggest that left and right amygdala may make different contributions to emotional retrieval processing.

A number of previous studies have reported either lateralisation of amygdala responses, or dissociable effects on emotional processing of damage to left and right amygdala, and the results of these experiments may illuminate the present findings. Morris and colleagues reported differential responsiveness of left and right amygdala respectively to 'masked' and 'unmasked' conditioned stimuli (Morris et al, 1998a, 1999) and to presentation of emotional faces to 'blind' and 'intact' visual hemifields of a patient with cortical 'blindsight' (Morris et al, 2001), suggesting that left amygdala may respond only to emotional stimuli of which subjects are consciously

aware, while right amygdala responses do not require awareness. Support for this view comes from the study of Gläscher and Adolphs (2003), who investigated SCRs elicited by 'masked' and 'unmasked' emotional photographs in patients with damage to left, right or bilateral amygdala. They reported reduced SCRs overall in patients with right and bilateral amygdala damage, which suggests that left amygdala either has limited influence on autonomic function, or that it responds only in a subset of emotionally-laden situation. In addition, SCRs correlated with ratings of arousal in normal subjects and right amygdala patients, but not in patients with left or bilateral amygdala damage (Gläscher and Adolphs, 2003). Together, these findings reveal a double dissociation between the effects of left and right amygdala lesions, and suggest that left amygdala decodes stimulus-specific emotional information, whereas right amygdala activity is triggered automatically by arousing stimuli, without the necessity for supraliminal processing.

An alternative laterality distinction was proposed by Funayama and colleagues (2001) based upon eyeblink startle responses to emotional pictures and to 'instructed fear' in patients with left and right temporal lobectomies. Damage to the right temporal lobe eliminated potentiation of startle responses to negative pictures, but not to threat trials in the instructed fear task, while patients with left temporal lobe damage showed normal startle responses to the emotional pictures, but not in the instructed fear task. The authors suggested that left amygdala may be specialised for verbally mediated emotional information, and right amygdala for visually conveyed emotion. It is difficult to separate these different proposals conclusively as the findings of Funayama and colleagues (2001) might reflect the fact that the instructed fear task requires awareness of, and appropriate reaction to, the association between stimulus and potential threat, while the findings of Morris et al (1998a, 1999, 2001) and

Gläscher and Adolphs (2003) could reflect the verbalisation of explicitly processed emotional stimuli. In either case, it seems parsimonious that our results reflect engagement of regions involved in the explicit processing of emotion, including left amygdala, if a recognised item elicits recollection of an emotional episode. In the absence of recollection changes in the emotional value of an item arising from its study history, which are insufficient to allow confident source judgements, may nevertheless result in a modulation of retrieval and emotional processing.

A role for left amygdala in explicit processing of emotional memories is consistent with data from human conditioning experiments indicating its involvement in situations where there is awareness of the contingency between an arbitrary stimulus and an unconditioned stimulus (UCS) (Büchel et al, 1999; Morris et al, 1998a), although other studies have reported bilateral (Büchel et al, 1998) or predominantly right amygdala activation (LaBar et al, 1998) using similar paradigms. Left amygdala have also been elicited in response to a stimulus subjects believed was associated with a risk of electric shock in an 'instructed fear' paradigm (Phelps et al, 2001), and by words previously encoded in negative vs. neutral sentences (Maratos et al, 2001).

The amygdala has also been associated with encoding of emotional information (Erk et al, 2003; Hamann et al, 1999). Reinstatement of encoding-related activity in sensory-specific cortices during retrieval has been proposed as reflecting recovery of particular elements of an engram, which are then bound into a coherent whole by episodic memory structures (see Nyberg et al. 2000; Wheeler et al. 2000; Vaidya et al. 2002; Gottfried et al, 2004). It is possible that the amygdala plays a similar role, representing the affective component of a memory trace, with its reactivation serving to 'tag' memories with representations of their behavioural significance. Amygdala activity at retrieval may also be important in enhancing re-encoding and

reconsolidation of emotional memories, contributing to their greater robustness over time compared to neutral memories (Cahill and McGaugh, 1998). This view is supported by findings that inhibition of protein synthesis in the amygdala after retrieval impairs reconsolidation, and later retrieval of fear memory (Nader et al, 2000).

The foregoing account predicts enhanced left amygdala effects, but not necessarily decreased right amygdala responses for source hit vs. source miss trials. There are a number of possibilities, the first of which is that the apparent right amygdala effects reflect differences in the baseline provided by the neutral source hit and miss conditions. If right amygdala activity provides an index of arousal, then the effects observed might reflect arousal differences between neutral source hit and miss trials. There were no significant differences in the normative arousal ratings for contexts which were hit or missed, although it cannot be ruled out that individual subjects were more likely to recollect those neutral contexts which they individually found more arousing, and hence the cues associated with them may have been able to elicit some right amygdala activity. Another potential reason for the differences observed is that cues which elicit recollection are arousing either because of the recollection itself, or because success on the source judgment task is rewarding. If such effects were to be sub-additive with emotion-induced arousal effects on right amygdala then the effects in this region could represent a subtraction artefact.

Other possibilities relate to allocation of cognitive resources and the wider networks engaged during emotional source hit and miss trials. Several studies have shown that activation of medial PFC can inhibit both sensory input to, and output from the basolateral amygdala (Grace and Rozenkranz, 2002; Rozenkranz and Grace, 2001), providing inhibitory feedback to amygdala and preventing inappropriate over-reaction

to emotional stimuli (Quirk and Gehlert, 2003). Medial PFC may also be crucial in amelioration and extinction of conditioned responses (Morgan et al, 2003). Recollection of emotional context generates enhanced activity in this region, which may inhibit amygdala responses - whilst right amygdala activity would decrease as a result, in left amygdala these inhibitory effects might be outweighed by recollection-induced facilitation of processing. An alternative possibility is that frontal activity inhibits the exogenous input to the amygdala, thus decreasing right amygdala activation, but does not interfere with representation of retrieved emotional information, which preferentially activates left amygdala (in accordance with the prevalence of left amygdala activations reported in emotional memory tasks e.g. Büchel et al, 1999; Dolan et al, 2000; Phelps et al, 2001; Maratos et al, 2001; Smith et al, 2004b).

In addition to amygdala effects, it was predicted that anterior insula would be more strongly engaged by emotional source hit than source miss trials. Interestingly, while this prediction was accurate, this region also showed greater activity for neutral source hits vs. misses, though emotional source hits were associated with significantly greater responses than their neutral counterparts. The insula has been previously associated with awareness of CS/UCS contingencies (Critchley et al, 2002), 'instructed fear' (Phelps et al, 2001), and retrieval of traumatic memories in patients with post-traumatic stress disorder (Liberzon et al, 2003). It also has a role in the processing of internally generated or interoceptive emotional information (Craig, 2003) and recall-induced generation of emotion (Damasio et al, 2000; Reiman et al, 1997). One possibility is that the insula may be responsive to the emotional assessment of internally represented information, such as a retrieved memory (see also chapter 2). Such effects may be observed even when assessing retrieved

information with little emotional significance, although activity is enhanced when the emotional content is higher.

Differences were also found in emotional effects elicited by source hit and miss trials in a range of other cortical areas. Interestingly, these were predominantly left-sided for source hit trials and right-sided for source miss trials, paralleling the scalp distribution of ERPs elicited by these trial types in a similar paradigm (chapter 4). As discussed earlier, the most prominent ERP effects emerged subsequent to attempted recollection, implying that the current results may reflect modulation of processes subsequent to retrieval attempt.

A considerable number of emotion effects on source hits were observed in areas also engaged by recollection of neutral memories in this, and other studies. These modulations probably reflect enhancement of processes supporting visual imagery, monitoring of the products of retrieval and guiding responses (see Smith et al, 2004b; chapter 5). Additionally, a number of regions associated with emotional processing, including ACC, OFC and VMPFC, were engaged by recollection of emotional contexts. ACC and VMPFC are often engaged during cognitively demanding emotion processing tasks and are candidate regions for integration of input from other emotion-responsive structures, allowing appropriate guidance of behaviour (Krawczyk, 2002; Phan et al, 2002). OFC is strongly associated with representing the affective value of stimuli (see Kringelbach and Rolls, 2004) and with emotion guided decision making (Bechara, 2004). These 'higher-order' emotion processing areas may be key in accurate source discrimination based upon retrieved emotional information.

For the source miss trials, explicit representations of emotional context or of the contingency between the object cue and the specific emotional context were not

retrieved. Nonetheless, aspects of the emotional significance of cues may be indexed in the brain. In addition to effects in right amygdala, activity was observed in extrastriate visual areas and fusiform gyrus, which may reflect re-entrant processing enhancing the visual analysis of arousing stimuli (Morris et al, 1998b). Likewise, effects in lingual gyrus, an important component of the semantic memory system (Price, 2000), may reflect enhanced semantic processing. It is possible that emotion effects in these areas are significantly greater for trials without accurate source retrieval as a result of different influences of left and right amygdala on these areas. Alternatively, when emotional information is accurately recollected and available for explicit emotion processing, it may be that attentional resources are directed towards the internal representation of the recollected context, rather than to processing of external stimuli.

Summary

The present findings demonstrate that retrieval activity reflecting test items' emotional study contexts can take two distinct forms, depending on the amount of information retrieved about the contexts. Recollection of an emotional episode engages a principally left fronto-temporal circuit, which may be important for interpreting the significance of retrieved memory, guidance of appropriate action, and may also contribute to enhancing re-encoding/consolidation of the engram. Stimuli previously associated with emotional contexts which fail to elicit recollection of specific emotional information may nonetheless undergo subtle changes in value, eliciting effects in right amygdala and areas processing visual and semantic aspects of the stimulus. Therefore two distinct circuits may be engaged to optimise the processing of stimuli which have acquired emotional value, and may facilitate the

ability to interpret and act upon retrieved material.

Chapter 8: Neural Interactions Underlying Retrieval of Emotional Memory

Introduction

In the previous chapters evidence for distinct neural processes underlying the retrieval of emotional and neutral memories has been discussed, and the brain regions involved in these processes highlighted. However, neural structures do not operate in isolation and cognitive processing depends on dynamic interactions between different brain regions. The primary aim of the present experiment was to investigate such interactions using dynamic causal modelling (DCM), a method for estimating the effective connectivity between different areas and how this is influenced by experimental factors.

In addition, two other issues about the effects of emotion on retrieval processing were addressed. Firstly, although retrieval of emotional information has been investigated under conditions when such information is task relevant and when it is not, it has yet to be determined whether the necessity to retrieve emotional information results in adoption of different cognitive strategies compared to when other contextual information must be retrieved. Evidence for activity during retrieval which is specific to the type of information to be retrieved, known as retrieval orientation, has been reported in ERP studies (e.g. Herron and Rugg, 2003; Herron and Wilding, 2004). For example, Herron and Wilding compared neural activity in a retrieval experiment where subjects, at test, were cued before each trial to perform one of three retrieval tasks, one requiring retrieval of semantic information, and the other two different types of episodic information. In order to obviate differences in activity arising from effects of retrieval *per se*, comparisons were made between activity in the interval

between task cueing and presentation of the word. They identified differences common to both episodic tasks compared to the semantic task (taken to reflect adoption of a 'retrieval mode', see chapter 1) and dissociable scalp topographies of old/new effects for the two episodic tasks, indicating the presence of retrieval orientation effects reflecting the particular type of information sought from memory.

In the present experiment, two different, interchanging source memory tasks were employed to investigate task effects, including retrieval orientation. In one task, subjects were required to make source judgments based upon whether the contexts with which an item was presented were negatively or neutrally valenced. In the second, subjects judged whether the context had contained people or not. Both these tasks require retrieval of salient aspects of the contexts, but the information on which the task depends differs, and may be reflected in retrieval activity. Task effects may take numerous different forms, and be revealed by different contrasts. Firstly, similar to the methods of Herron and Wilding (2004), activity during a cueing period can be compared, revealing potential differences in a tonically adopted cognitive set, presumably facilitating retrieval of task-relevant information. Secondly, activity can be compared during performance on the two different source tasks. Effects revealed by such a contrast may again fall into two categories. Firstly, there may be specific search strategies adopted for relevant source memory once an item is presented or recognised. Adoption of such strategies will not be indexed by activity during task switching instructions but will, at least, be present for all items believed to be old during a particular task. Additionally, some task effects may reflect facilitated post-retrieval processing of task relevant information. In the present study, for example, during the emotion discrimination task some effects which distinguish retrieval of

items from emotional and neutral contexts might be enhanced, facilitating their discrimination in the behavioural task.

In addition to the task effects discussed, it was of interest whether some of the effects observed, either behavioural facilitation or processing differences, are due to differences in the ease of the encoding task for emotional and neutral contexts. In the present experiment such differences were tested for by measuring the time taken to make connections between critical objects and their contexts during encoding.

Before describing the specific methods employed in this experiment, connectivity analysis and specifically DCM will be discussed.

Connectivity Analysis

Interactions between brain regions underlie all cognitive processes, and have been investigated using a number of techniques, including PET (e.g. McIntosh and Gonzalez-Lima, 1991; McIntosh et al, 1994), fMRI (e.g. Lowe et al, 1998; Mechelli et al, 2002) and EEG (e.g. Pfurtscheller and Andrew, 1999; Fell et al, 2001).

Haemodynamic measures of brain activity have been used in a variety of analyses investigating effective connectivity between brain regions. At the cellular level, effective connectivity has been defined as the simplest circuit which can produce the same temporal relationship as observed experimentally between two neurons in a cell assembly, which can be extrapolated to the relationship between two anatomically distinct brain regions. However, multiple arrangements of interacting brain regions may lead to the same pattern of results (see Friston, 1994; Horwitz, 2003 for further discussion of functional and effective connectivity). A wide range of methods have been used to examine connectivity, from simple correlation of activity in different

regions to complex models of brain networks using techniques such as structural equation modelling (SEM). For example, Büchel and Friston (1997) used SEM to demonstrate that increasing attention to a moving visual stimulus led to increased connectivity from visual area V5 to the posterior parietal cortex, and were able to attribute this effect to an influence of PFC on V5 afferents to posterior parietal cortex. These techniques allow questions about brain function to be explored in a more biologically plausible way than standard functional segregation analyses.

DCM differs from other types of connectivity analysis in two important ways. DCM aims to construct a model of interacting cortical regions which, together with a forward model describing the transformation of activity into a measured response (such as the BOLD signal), aims to explain the observed data. This approach is a fundamental departure from other techniques, such as SEM or autoregression models, which assume that observed responses are driven by endogenous noise, while DCM assumes the responses to result from designed perturbations of the modelled system (i.e. experimental factors). Secondly, many 'conventional' approaches are limited to modelling linear interactions between brain areas, and may also be static models, failing to capture the dynamic changes in these interactions. DCM accommodates the non-linear and dynamic nature of neural interactions. Some basic details of how DCM is performed will now be discussed.

Dynamic Causal Modelling

DCM treats the brain as a deterministic and dynamic system, where external inputs cause changes in neuronal activity, which in turn leads to changes in the observed signal. It should be noted that DCM is not limited to haemodynamic models of neural

activity, but combines a neurodynamic model, predicting changes at the level of the brain itself, together with a modality specific forward model, describing the transformation of the neural activity into observable data. For fMRI data, an extended Balloon model describes the haemodynamic changes induced by effects at the neural level (see Friston et al, 2003). The crucial aspect of DCM however, is estimation of the parameters of the neurodynamic model, which is described by a multivariate differential equation :

$$\dot{z}_t = \left(A_u + \sum_{j=1}^{M} u_t(j) B_u^j \right) z_t + C u_t$$

where z_t describes neural activity and u_t the input state at time t. The rate of change of activity over time, $\dot{z}_t$, is linearly dependent on the product of z_t and $u_{t,,}$ with this multiplicative combination of factors endowing the model with nonlinear dynamics.

As can be seen from the equation above, the model is described in terms of 3 sets of parameters, A, B and C, about which inferences may be drawn. The matrix of parameters, A, describes the set of intrinsic connections between the regions specified in the model, in terms of which regions are connected, and whether they are unidirectional or bidirectional. The actual values of the connections are specific to the experiment, rather than reflecting a generalised baseline connectivity. All DCMs incorporate self-connections for each area, with prior distributions that constrain these values as being negative such that, in the absence of inputs to the model system, neural activity will decay over time. The effects of inputs on the different structures in a DCM are described by the C matrix, with typically only one or two regions receiving direct input. In effect, a classical SPM analysis can be mimicked by a DCM with zero connectivity between regions, and direct input to every area. Probably the

most interesting parameters are the modulatory parameters B^j, describing which intrinsic connections can be modulated by which inputs. Note that 'inputs' consist of both experimental trials and cognitive sets so that, in the current experiment for example, both visual retrieval cues and the type of retrieval task attempted during the current block are inputs to the system.

The model structure is defined by specifying which parameters in the A, B and C matrices can take on non-zero values. These matrices are concatenated with the haemodynamic parameters derived from the Balloon model to form a vector containing all the parameters describing the transformation of input states to observed data.

These parameters are then entered into an iterative expectation-maximisation (EM) algorithm in order to estimate the model (see Friston et al, 2003). As DCM uses a Bayesian framework, the likelihood distribution (reflecting the probability of the data given a particular parameter set) is combined with the prior expectation of the parameters to determine the 'posterior density' (the probability of the parameter set given the data). Therefore DCM incorporates priors on both haemodynamic parameters (which are empirically determined, with only two linear mixtures of the parameters allowed in order to reduce the computational load of estimation) and the coupling parameters. Some of these priors are set during model design, such that possible connections not included in the model have prior mean and variance of zero. Other constraints on the priors reflect the fact that in real neuronal systems activity will not diverge exponentially, and must return to a stable mode in the absence of input. The priors chosen ensure negative self-connections for each region, relating to intrinsic decay or self-inhibition, and keeping the system stable (for more detail on how this is done see Friston et al, 2003).

For most processes modelled with DCM, there are likely to be multiple plausible models which can be estimated. Even with prior knowledge about anatomical connectivity and functional roles of different brain regions, it is likely that multiple models will be tested, raising the question of how to select the best model. Although it is possible to visualise the predicted fMRI (or other) signal generated by a particular DCM, and compare this to the observed data in each region of interest, such a method is both subjective and also fails to account for the fact that increasing the complexity of a model will tend to improve model fit, even if the model itself becomes less parsimonious. It is difficult to compare models employing different numbers of brain regions in the way described below so subjective judgments may be used, but models with the same number of areas can be compared using the 'model evidence'. This is computed from:

$$p(y \mid m) = \int p(y \mid \theta , m) p(\theta \mid m) d \theta$$

Where y is the observed data, m is the model and θ is the combined vector of neuronal and haemodynamic parameters. This equation can be transformed using the Laplace approximation, and re-expressed as:

$$\log p(y \mid m)L = \text{Accuracy (m)} - \text{Complexity (m)}$$

(see Penny et al, 2004 for the proof of this transformation)

However, the Laplace approximation is strongly dependent on the priors of the model, and as these are relatively strong to assist convergence to a stable model with plausible neuronal dynamics, it becomes difficult to compare models with different numbers of connections. Two alternative approximations are instead used to compute model evidence. The first of these, the Bayesian Information Criterion (BIC) is a special case of the Laplace approximation, while the second Akaike's Information

Criterion (AIC) is maximised when the approximation of a novel data point is closest to the true likelihood. The main difference between these two measures is the cost of complexity – BIC has a higher parameter cost than AIC and is thus relatively biased towards simple models, while AIC is biased towards complex models (Jefferys, 1935 cf. Penny et al, 2004).

Bayes factors comparing models i and j are calculated as:

$$B_{ij} = \frac{p(y \mid m = i)}{p(y \mid m = j)}$$

such that B_{ij} is a relative probability, where $B_{ij} < 1$ favours model j and $B_{ij} > 1$ favours model i. In the present experiment, there was judged to be consistent evidence in favour of one model over another if both AIC and BIC approximations produced Bayes factors of e or greater. Where not all subjects favour the same model an overall Bayes factor can be calculated across subjects by multiplying the lower of the two Bayes factors for each model comparison. This acts as a safeguard against a model with a small advantage in a large proportion of subjects being chosen when another model is strongly favoured in significant minority of subjects.

Methods

Subjects

Sixteen (eight female) right handed young adults (age range 19-30 years, mean 24) were employed as subjects and remunerated at £7.50/hour. All were in good health with no history of neurological or psychiatric illness. The experiment was approved

by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

Stimulus Materials and List Construction

The critical objects employed in this experiment were identical to those described in chapter 3b, except that only 320 of the 360 objects were employed, to simplify counterbalancing. A combination of IAPS and other photographs were used as encoding contexts, factored according to whether they were negatively or neutrally valenced and whether or not they contained people. Forty photographs were selected for each of four categories: neutral with people, neutral without people, negative with people and negative without people, for a total of 160 encoding contexts. The slides containing people were balanced across valences in terms of the total number of people across all the contexts, the number of male and females, and the number of contexts depicting individuals, small groups or large groups of people.

Eight study lists, similar to those employed in the earlier experiments described, were formed with each critical object being associated with a neutral context containing people in one list, neutral without people in a second, negative with people in a third and a negative context not containing people in a fourth list. The contexts were ordered pseudorandomly, with the constraint that no more than 3 consecutive slides could be of the same valence or contain/not contain people. The objects were each then absent from four of the eight study lists, and were available as new items for the corresponding test lists. Each study list had 2 associated test lists incorporating the 160 old items, 80 new items and 60 'null events'. These were divided into twenty-four 'blocks' of ten events each during which subjects would perform either an

emotional source judgment or a people source judgment. The different classes of test event (4 types of old item, new items and null events) were counterbalanced across the two classes of test block. The order of task blocks was pseudorandom, with no more than 2 blocks of one task being presented consecutively.

Study Procedure

In the study phase, stimuli were presented via a mirror mounted on the head coil of the fMRI scanner, in direct view of the supine participant, at a distance of approximately 50cm from the projection screen. The background was initially presented alone on the screen for 3s. 3s after presentation of the context, the critical object was superimposed centrally upon the background, and subjects were required to imagine a connection between background and object. This connection was made covertly, but subjects were required to respond with a keypress once they had made a connection successfully. The object and background were presented together for 4.5s, and the screen was then blanked for 750ms before presentation of the next background. Eight practice trials were given prior to the study proper, during which the subjects were required to describe verbally the connections they had made between background and object, thereby ensuring they understood the task. During the study phase proper, a rest break was given after 80 trials.

Test Procedure

The test phase followed the study phase after a delay of five minutes, during which a serial subtraction task was performed to prevent rehearsal. Stimulus delivery used the same setup as during study. A white asterisk was presented against a black

background for 500ms, following which the test item was presented for 1500ms. This was followed by a white fixation cross on a black background for 2200ms before presentation of the asterisk denoted the imminent onset of a new trial. This sequence of events gave a stimulus onset asynchrony (SOA) of 4200ms. 60 'null events', consisting of the white fixation cross for an additional 2s in place of the white asterisk and test item, were incorporated into the test list, allowing estimation of baseline. Subjects were instructed to respond, as quickly and accurately as possible, with one of four buttons, depending on the task. In both tasks, one button indicated that the object was being seen for the first time (new) and another that the subject knew the object was old but could not remember the background with which it had been paired at study. The third and fourth buttons were for source judgment responses, which were task-dependent. During blocks of the emotion discrimination task subjects discriminated between recollected contexts in terms of whether they were neutrally or negatively valenced, and regardless of whether or not they had contained people. In the people discrimination task, subjects discriminated contexts on the basis of whether or not they contained people, regardless of the valence of those contexts. These tasks were performed in blocks, with an instruction being presented on the screen for 10s prior to the start of each block informing subjects as to the task to be undertaken in the following block.

The test list was split into 2 equal parts, with each part containing twelve task blocks. Prior to the test phase proper an example test phase was given, containing the 8 items from the practice study list, plus 4 new items, with half tested on the emotion discrimination and half on the people discrimination task. None of these items appeared in the subsequent test list.

Imaging and Image Processing

MRI data were acquired from a 1.5T Siemens SONATA system (Siemens, Erlangen, Germany) equipped with a head coil. Functional images were acquired with a gradient echo-planar T2* sequence using BOLD (blood oxygenation level dependent) contrast, with a repetition time (TR) = 1.96.s, giving an effective sampling rate of approximately 8Hz at both study and test. A series of z-shims were employed to minimize signal loss and distortion in medial temporal regions, at the cost of signal loss in posterior lateral temporal regions. 22 slices of 2mm thickness were acquired, with an inter-slice gap of 1.3mm. This gave limited coverage of the brain, ranging from approximately $-22 < Z < 50$ on the Talaraich and Tournoux (1998) coordinate system. Data were acquired during four separate sessions (two each at study and test) with the first five volumes of each session discarded to allow for T1 equilibration effects. Images were realigned, unwarped, normalised to a standard echo-planar image template and smoothed with a Gaussian kernel with full-width half maximum of 8mm.

Statistical Analysis of Images

Initially, data were analysed using Statistical Parametric Mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, UK; Friston et al, 1995) using a random-effects analysis. Test data were modeled as 14 discrete event types: old items from each of the 4 categories of old items (neutral with people, neutral without people, negative with people, negative without people) were separated according to whether they received correct source judgments (source hits), received either 'old, but source unknown' or incorrect source judgments (source misses) or were incorrectly

judged to be new (misses); new items were separated into those which were correctly rejected as new (correct rejections), or incorrectly judged to be old (false alarms). A separate regressor of no interest was formed for those trials where no response was logged, or where no successful connection had been made during encoding. Principal contrasts were between those events which received correct responses (i.e. source hits, source misses and correct rejections).

Regressors modelling events were convolved with a standard canonical haemodynamic response function. Linear contrasts of parameter estimates were estimated for each subject, and initial statistical parametric maps were generated. For some contrasts, hits were collapsed across one or other of the experimental factors (such that 'negative hits' were collapsed across trials employing negative contexts which had or had not contained people). Task factors were modelled by convolving a box-car function with a standard HRF. The epochs during which subjects performed either emotion or people discrimination tasks were contrasted, as were those for the inter-block instruction periods.

Principle contrasts were all based on one-tailed t-tests, either using a threshold of $p < 0.05$, volume corrected for the entire brain, or uncorrected with a significance level of $p<0.001$ (uncorrected) and a spatial extent threshold of at least 5 contiguous voxels ($k=5$).

Statistical Analysis – Dynamic Causal Modelling

Based upon the random effects analyses and previous findings we selected four regions to form our dynamic causal model. These areas were a region of visual fusiform cortex, acting as a visual input area to the model system, the hippocampus,

the amygdala and medial orbitofrontal cortex. fMRI signal was extracted from these regions of a subject by subject basis. Each region of interest consisted of a sphere of 6mm radius centred around the local maximum of each subject closest to the peak coordinates from the random effects analysis in the appropriate region. The closest maximum was chosen in each case so long as it was within 16mm (i.e. twice the FWHM of the smoothing kernel) of the random effects peak and was identified as being within the appropriate brain region on each subject's normalised structural scan. The coordinates of these areas in each subject are given in table 8.1.

A number of different models were set up and estimated for each subject, either including the OFC or not, and allowing different intrinsic connections between brain areas and different effects of task and contextual factors on the input and connectivity

Subject	Fusiform gyrus	Amygdala	Hippocampus	Orbitofrontal cortex
RFx mean	-42, -66, -15	-24, -6, -15	-30, -24, -6	-3, 48, -21
1	-42, -66, -15	-24, -3, -18	-33, -27, -9	-6, 57, -18
2	-45, -69, -12	-27, -6, -15	-27, -24, -12	-6, 42, -24
3	-42, -66, -15	-21,0,-15	-30,-24,-9	-3,51,-21
4	-48,-60,-12	-24,-6,-15	-27, -18, -12	-9,39,-24
5	-42,-69,-12	-27,-3,-18	-27,-30,-6	-6,51,-24
6	-39,-66,-12	-24,-6,-15	-30,-24,-12	-3,42,-21
7	-39,-69,-15	-27, -9, -15	-30, -24, -6	-3,57,-9
8	-45,-66,-12	-24,-6,-12	-27,-21,-9	-3,51,-27
9	-42,-69,-12	-21,-6,-15	-33,-24,-9	-6,42,-24
10	-39,-66,-15	-21,-3,-15	-36,-24,-6	-3,57,-9
11	-45,-63,-12	-24,-6,-18	-27,-18,-9	-3,42,-21
12	-48,-66,-15	-27,-3,-15	-30,-21,-9	-6,51,-24
13	-42,-63,-12	-24,-6,-18	-30,-21,-12	-6,45,-24
14	-45,-66,-15	-21,0,-15	-24,-18,-9	-9,45,-24
15	-42,-66,-15	-24,-3,-18	-27,-21,-9	-3,42,-21
16	-48,-69,-12	-18,-6,-15	-30,-24,-12	-3,51,-21

Table 8.1 Peak coordinates of the regions used for the dynamic causal model in each subject, together with the group mean from the random effects analyses

modulation parameters. The most parsimonious model was selected as that which, across subjects, generated predictions which modelled the observed data most accurately. Across models employing different numbers of areas model selection was done by visual inspection of observed and predicted data, while for models employing the same brain regions this was complemented by using Bayesian model selection, comparing the AIC and BIC for each model. Subject specific input and coupling parameters were estimated and entered into a series of paired t-tests to compare experimental effects on these parameters across subjects.

Results

Behaviour

Recognition accuracy and associated reaction times (RTs) are shown in table 8.2, together with accuracy for source judgements to old items, and the time taken to form connections between objects and contexts at encoding. ANOVA of hit rates revealed that items encoded in negatively valenced contexts were more likely to be recognised than those from neutral contexts [$F(1, 15) = 5.62$; $p < 0.05$], whilst items associated with contexts containing people were more likely to be recognised than those associated with contexts devoid of people [$F(1,15) = 4.75$; $p<0.05$]. Emotion and people factors did not show a significant interaction in terms of their effects on hit rates. Recognised items were more likely to have their source correctly attributed if they had been encoded in a negative context [$F(1,15) = 8.06$; $p <0.05$] and if from a context containing people [$F(1,15) = 11.15$; $p < 0.01$]. These factors showed a significant interaction [$F(1,17) = 5.17$; $p < 0.05$], reflecting the fact that items encoded

Table 8.2 Mean accuracies and reaction times (Standard deviations in parentheses)
P+ indicates items from contexts containing people, and P- those from contexts which did not.
Study RTs averaged from 14/16 subjects due to logging failure in remaining 2 subjects.

	Neutral P+	Neutral P-	Negative P+	Negative P-	Correct Rejection
Hit accuracy	0.89 (0.07)	0.86 (0.09)	0.93 (0.07)	0.88 (0.08)	0.89 (0.07)
Source accuracy	0.60 (0.11)	0.56 (0.11)	0.70 (0.12)	0.58 (0.06)	-
Retrieval RT (ms)	1978 (327)	1949 (298)	1937 (385)	2012 (309)	1367 (249)
Encoding RT (ms)	6483 (311)	6541 (327)	6484 (325)	6563 (289)	-

in negatively valenced contexts containing people were much more likely to attract correct source judgements than those from any other contexts. There were no significant differences in RTs to hits.

In order to elucidate the possible reasons for the observed accuracy differences, additional analyses were performed comparing the speed at which successful connections between object and context were formed during encoding (assumed to reflect the ease of association) and the valence and arousal scores attributed to the contexts by pilot subjects during material selection. ANOVA of study RTs revealed no significant effects of negative vs. neutral valence, but did show that subjects formed object-context associations more rapidly when contexts included people than when they did not [$F(1,13) = 5.99$; $p < 0.05$]. Negative contexts were rated as more negative and more arousing than their neutral counterparts (both $F>100$). The presence or absence of people did not affect valence [$F(1,5) = 1.03$;ns] or arousal [$F(1,5) = 1.16$; ns] ratings for neutral contexts, but negative contexts containing people were rated as both more unpleasant [$F(1,5) = 10.65$; $p<0.05$] and more arousing [$F(1,5) = 49.09$; $p < 0.001$] than those which did not.

fMRI Random Effects Analyses - Retrieval effects

An *inclusive* mask incorporating the outcomes of contrasts between source hits and correct rejections from neutral and negative conditions revealed activity common to successful retrieval of emotional and neutral source memories (table 8.3). Significant effects were evident in large regions of left lateral parietal and prefrontal cortex and bilateral cuneus and posterior cingulate. More restricted areas of right parietal and prefrontal cortex also showed significant old/new effects. These findings correspond to those reported in other event-related fMRI studies of source memory (Henson et al, 1999; Rugg et al, 2002), and those found in the previous experiment (chapter 7). Further effects were identified in diencephalic and basal ganglia structures.

	Region			Peak Coordinates			Peak Z-score	
			Voxels	x	y	Z		
L/R	Cuneus/Posterior cingulate	(BA 7/23)	219	-12	-69	30	5.58	*
				(9	-57	15)		
				(9	-72	33)		
L	Cuneus	(BA 30)	13	-9	-60	9	3.69	
L	Superior/Inferior Parietal lobule	(BA 7/40)	183	-33	-72	48	5.14	*
				(-33	-57	42)		
				(-36	-45	33)		
R	Superior Parietal lobule	(BA 7)	17	36	-69	47	3.74	
L	Posterior cingulate	(BA 29)	16	-9	-45	15	3.74	
L/R	Thalamus/Caudate		71	-9	-3	3	4.34	
				(9	12	3)		
L	Middle frontal gyrus	(BA 9/46)	305	-42	21	27	5.41	*
				(-54	21	30)		
R	Middle frontal gyrus	(BA 46)	31	45	27	24	4.20	
L	Inferior frontal gyrus	(BA 47)	155	-30	30	-3	5.30	*

Table 8.3 Common old/new effects for all classes of old item vs. correct rejections, independent of retrieval task ($p < 0.001$, uncorrected, $k = 5$). Coordinates in brackets are secondary maxima within clusters. * indicates areas surviving correction for whole brain volume (FWE) at $p < 0.05$

Emotion Effects

Contrasts between emotional and neutral source hits (collapsed across retrieval task) revealed (table 8.4; fig 8.1) that retrieval of emotional contexts was associated with increased activity in left amygdala and surrounding areas of periamygdaloid/ parahippocampal cortex. Enhanced activity was also seen in bilateral prefrontal cortex, cuneus, posterior cingulate, hypothalamus and brainstem, together with left lingual gyrus, cerebellum, supramarginal gyrus and thalamus. Other regions showing were the right middle temporal gyrus, lateral globus pallidus and claustrum. Using an

	Region			Peak Coordinates			Peak Z-score	
			Voxels	X	y	z		
R	Cuneus	(BA 18)	16	21	-87	27	3.92	
L	Cuneus	(BA 17)	21	-12	-75	12	3.90	£
R	Posterior Cingulate	(BA 30)	14	6	-69	9	3.97	
L	Posterior Cingulate	(BA 31)	41	-3	-57	24	3.99	£
L	Lingual gyrus	(BA 19)	28	-18	-60	0	4.92	*
L	Cerebellum		28	-48	-51	-21	4.32	
L	Supramarginal gyrus	(BA 40)	30	-60	-45	21	4.46	
R	Middle temporal gyrus	(BA 21)	29	60	-18	-6	4.23	
L	Pons		20	-9	-18	-24	4.39	
L/R	Hypothalamus		14	-3	0	-6	4.41	
L	Thalamus		5	-6	-12	9	4.48	
R	Lateral globus pallidus		25	21	-6	-6	4.78	*
L	Amygdala/Parahippocampal gyrus		114	-30	3	-21	5.42	*
				(-24	-3	-18)		
				(-18	3	-18)		
R	Claustrum		25	27	15	-6	4.61	
L	Inferior frontal gyrus	(BA 45)	7	-57	18	6	4.88	*
		(BA 47)	39	-33	30	-18	4.44	£
R	Inferior frontal gyrus	(BA 47)	26	36	27	-6	4.61	

Table 8.4 Brain regions identified in the contrast between items attracting correct source judgments from negative vs. neutral contexts, independent of retrieval task. £ indicates regions surviving inclusive masking with the contrast of neutral source hits with correct rejections. Others as above.

inclusive mask it was identified that some of the emotion effects in left cuneus, posterior cingulate and prefrontal cortex overlapped with old/new effects identified above, suggesting that they may reflect modulation of processes engaged by retrieval of both neutral and emotional memories. Note that contrasting activity associated with items attracting source hits encoded in neutral backgrounds with vs. without people failed to show any significant effects, further suggesting that the observed effects are emotion specific.

Task-related Effects

A number of regions discriminated between whether subjects were attempting to categorise retrieved memories according to whether the associated contexts had been negative or neutral (emotion task) or whether they had or had not contained people (people task). The emotion task was associated with greater activity in bilateral temporal lobe regions, including both left and right amygdala and left hippocampus. Additional effects were revealed in bilateral prefrontal areas, including medial orbitofrontal cortex and VMPFC, the left anterior insula, caudate and bilateral thalamic areas, as well as the brainstem (table 8.5, fig 8.2). The reverse contrast revealed a region of right middle temporal gyrus which was more active during the people than the emotion task.

Task-switching Effects

Several regions showed differential activity during the instruction periods leading up to each test block. These effects may reflect preparatory or strategic processes prior to retrieval attempts. When subjects were cued that the next task block would involve

the emotion rather than people discrimination task, there were significant increases in BOLD signal in right precuneus, bilateral inferior parietal lobe and right PFC. The reverse contrast revealed effects in bilateral middle temporal gyrus, right parahippocampal gyrus and left PFC (table 8.6).

	Region			Peak Coordinates			Z-score	
			Voxels	x	y	z		
Em > Peop								
L	Posterior Cingulate	(BA 31)	11	-6	-66	24	4.15	$
L	Inferior Parietal Cortex	(BA 7)	21	-36	-63	39	3.89	£
R	Superior temporal gyrus	(BA 22)	43	45	-57	15	4.48	
L	Supramarginal gyrus	(BA 40)	23	-39	-42	33	4.48	
R	Midbrain (SN)		49	12	-21	-9	5.01	*
L/R	Thalamus		61	3	-21	12	4.75	
L	Hippocampus		15	-30	-21	-6	4.25	
R	Inferior temporal gyrus	(BA 20)	14	48	-9	-21	4.83	
R	Anterior temporal lobe	(BA 20)	11	30	-6	-39	4.30	
L	Anterior temporal lobe	(BA 36)	23	-27	-6	-33	4.08	
L	Amygdala		42	-24	-6	-15	4.28	$
R	Amygdala/Parahippcampal gyrus		54	36	-6	-15	5.19	
				(24	-3	-15)		
L	Caudate body		20	-15	-6	24	4.69	
L	Anterior Insula	(BA 13)	49	-39	15	3	4.65	
R	Inferior frontal gyrus	(BA 47)	89	42	33	-9	5.17	*
L	Middle/Inferior frontal gyrus	(BA 11/45)	158	-42	36	-12	5.63	* $
				(-54	21	6)		
L/R	Medial orbitofrontal cortex	(BA 11)	42	-3	48	-21	4.93	*
L	Medial frontal gyrus	(BA 9)	31	-6	48	15	3.96	
				(-3	51	33)		
Peop > Em								
R	Middle temporal gyrus	(BA 19)	32	36	-60	12	5.1	*

Table 8.5 Brain regions discriminating between performance of emotion and people discrimination tasks. $ indicates regions surviving inclusive masking with the contrast of negative and neutral source hits. Other symbols as above.

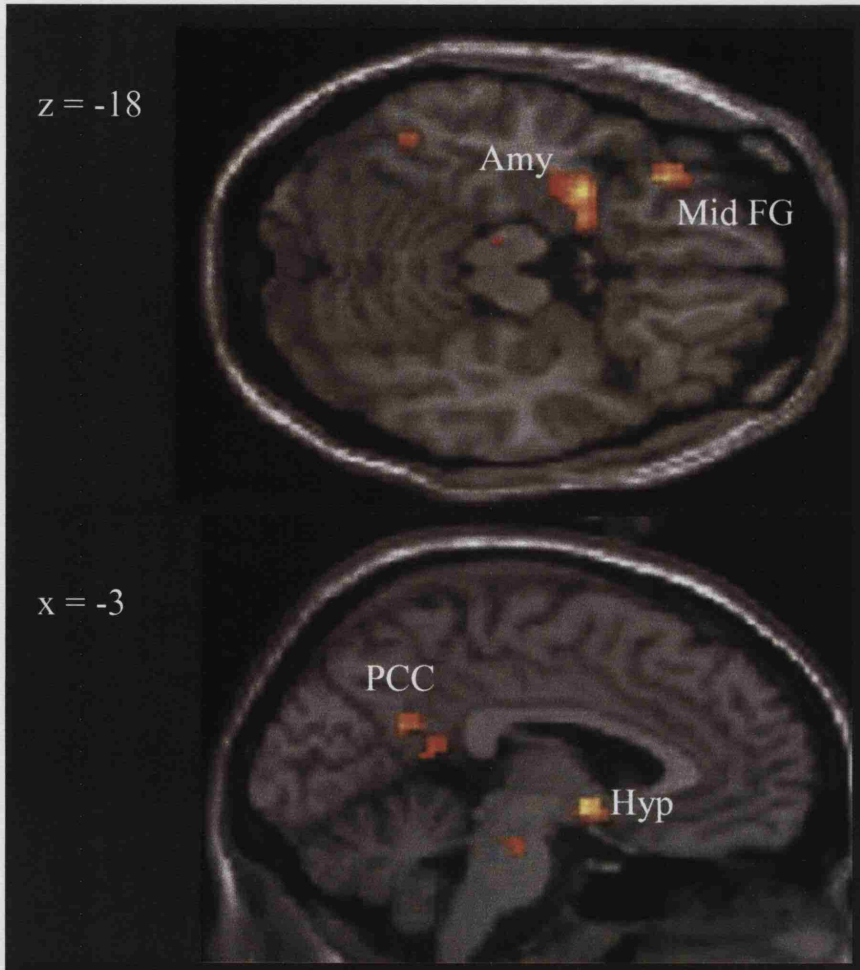

Figure 8.1. Selected brain regions showing enhanced activity for negative vs. neutral source hits, independent of task (shown at $p < 0.001$, uncorrected. $k = 5$). Activity peaks are highlighted for amygdala (Amy), middle frontal gyrus (Mid FG), hypothalamus (Hyp) and posterior cingulate cortex (PCC).

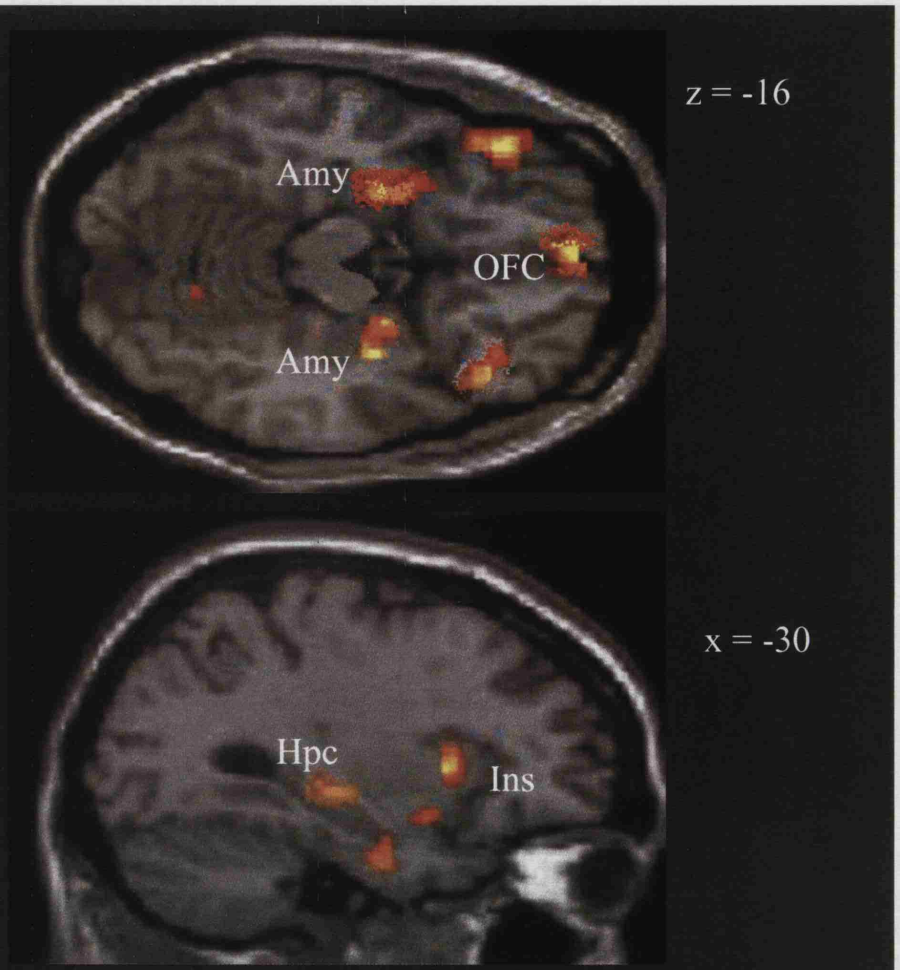

Figure 8.2. Brain regions more active during emotion than people source discrimination tasks. Highlighted areas are orbitofrontal cortex (OFC), hippocampus (Hpc), anterior insula (Ins) and amygdala (Amy).

	Region		Voxels	Peak Coordinates X	y	z	Z-score	
Emotion switch cue > People switch cue								
R	Precuneus	(BA 7)	8	3	-72	51	3.78	
L	Inferior parietal lobule	(BA 7/39)	31	-36	-63	42	3.83	£
R	Inferior parietal lobule	(BA 40)	28	36	-48	48	3.71	
R	Middle Frontal Gyrus	(BA 9)	48	39	15	30	4.52	
			22	36	33	33	3.99	
People switch cue > Emotion switch cue								
R	Middle temporal gyrus	(BA 39)	5	45	-66	18	3.44	
L	Middle temporal gyrus	(BA 39)	5	-45	-57	24	3.42	
R	Parahippocampal gyrus	(BA 36)	8	27	-39	9	3.78	
L	Superior Frontal Gyrus	(BA 10)	15	-24	54	12	4.02	

Table 8.6 Brain regions discriminating between pre-task instruction periods.

Dynamic Causal Modelling

Based upon *a priori* expectations of areas involved in retrieval of emotional memory, the results from the standard analyses presented above and model fit a dynamic causal model (DCM), incorporating left fusiform gyrus (acting as a visual input region), hippocampus, amygdala and OFC, was generated. A number of models were formed and estimated, incorporating different combinations of forward and back connections, and allowing different influences of task factors upon the model parameters. The most parsimonious model (illustrated in fig. 8.3) as determined by Bayesian model selection provided the best fit of the data in 15/16 subjects, with an overall Bayes factor of 9.3×10^{10} relative to the model favoured in the remaining subject. Paired t-tests across subjects on the parameters reflecting changes in connectivity induced by experimental factors revealed that negative source hits were associated with greater increases in connectivity from fusiform gyrus to hippocampus ($t_{15} = 2.47$, $p < 0.05$) and from hippocampus to amygdala ($t_{15} = 2.30$, $p < 0.05$). When emotional

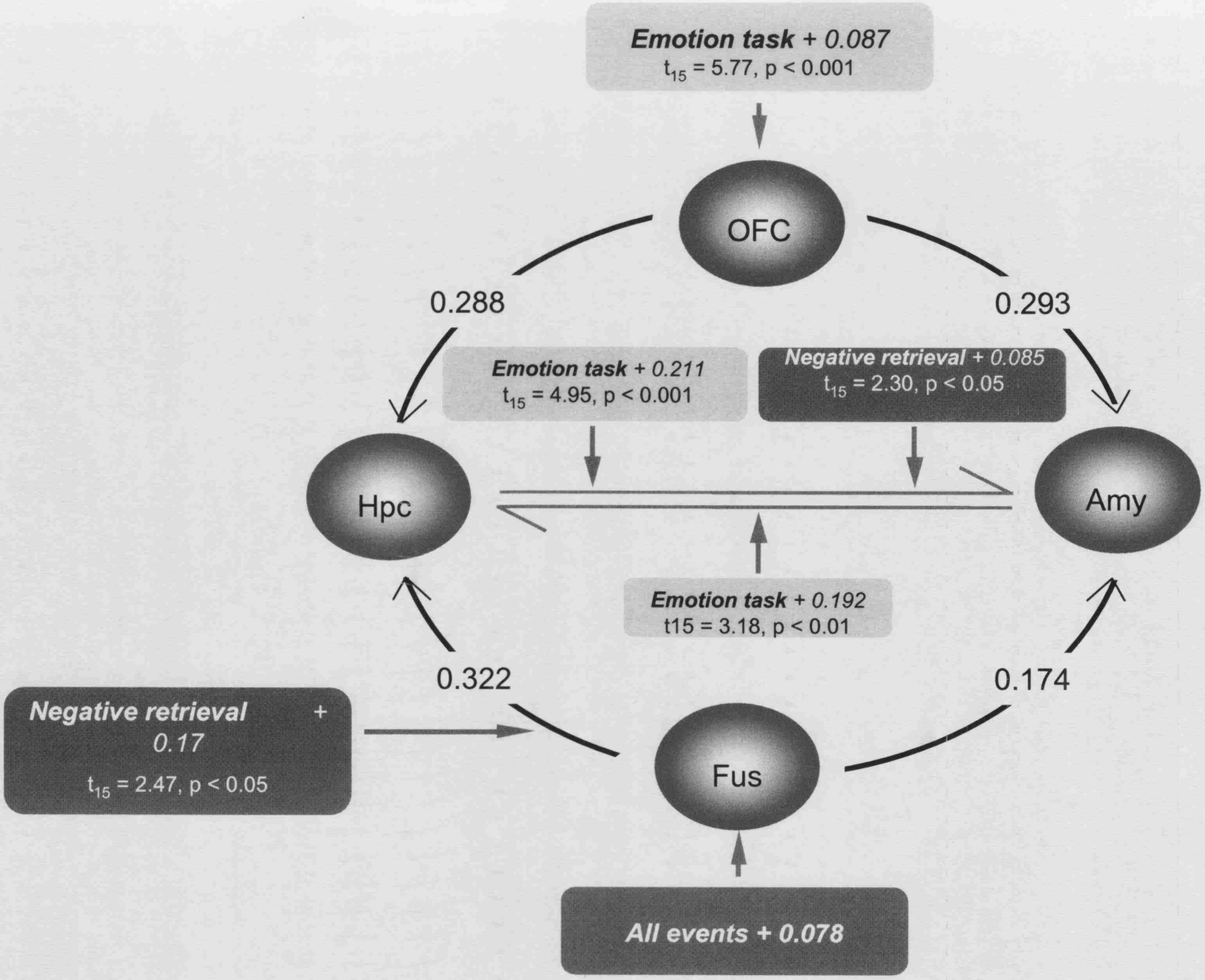

Figure 8.2. Dynamic causal model of the interactions between visual fusiform cortex (Fus), hippocampus (Hpc), amygdala (Amy) and orbitofrontal cortex (OFC). Significant changes in connection strength associated with item type (dark grey) and behavioural requirements (light grey) are given for each connection.

contextual information was relevant to the source judgement task there was increased modulation of OFC activity ($t_{15} = 5.77$, $p < 0.001$) and of the connectivity both from hippocampus to amygdala ($t_{15} = 4.95$, $p < 0.001$) and amygdala to hippocampus ($t_{15} = 3.18$, $p < 0.01$).

Discussion

Behaviour

Items associated with contexts either containing people or negatively valenced were both more likely to be recognised and to attract accurate source judgments. One possibility is that presence of either emotional content or people in contexts make them more salient, and that this salience leads to the observed behavioural effects. However, as the encoding task was easier to perform when contexts contained people, it may be that the differences arising from contexts with or without people reflect differences in encoding task difficulty. In any case, improved source memory for emotional contexts was observed, as in the previous experiments described. The degree of this enhancement may correlate with the valence or arousal of the contexts. This is suggested by the greater enhancement of memory for negative items containing people than not containing people than the equivalent difference for neutral contexts. As negative contexts containing people were, on average, more unpleasant and more arousing than those which did not this may explain the additional enhancement of memory (but see valence effects in chapter 6).

fMRI Retrieval Effects

The regions identified in the random effects analysis as being involved in retrieval of neutral and emotional source memories were similar to those seen in the previous experiments described. As in chapter 7, these effects identified brain regions reported in previous studies of source memory for emotionally neutral material (e.g. Henson et al, 1999; Rugg et al, 2002), complemented by other areas more commonly associated with emotional processing. Previously it was suggested that engagement of these additional areas might occur as a result of the requirement to retrieve emotional information for the source task. This is consistent with the task effects findings (see below) which show that the thalamic and caudate regions engaged by retrieval of each class of old items are more active during the emotion discrimination task than the people task.

Emotion Effects

As in the previous experiments described, retrieval of emotional memories was associated both with enhanced activity in structures supporting retrieval of neutral memories, and additional activity in structures associated with emotional processing, including the amygdala and prefrontal regions. As these findings were similar to those reported in the earlier experiments, they will not be discussed further here.

Task Effects

There were significant differences in the neural activity associated with performing emotion and people discrimination tasks, both during the tasks themselves and when

cued as to the task requirements. As discussed earlier in the chapter, these effects may be due to different influences of the task on retrieval and para-retrieval activity. Firstly, subjects may adopt alternative retrieval strategies or orientations when the task requires retrieval of different types of information from memory, with such effects either being constant throughout the task block, or being engaged only for appropriate trials. Secondly, the task factor may interact with retrieval or post-retrieval processes associated with recollection of particular types of information. There were no differences in recognition or source memory performance on the two tasks, so task effects do not simply reflect a different balance of trials in emotional and neutral tasks, but it may be that emotion effects are enhanced when the retrieved information is task relevant.

Differential activity during the instruction block periods most likely reflects adoption of a tonic retrieval state, which may facilitate the retrieval of task-appropriate information. None of the areas revealed by this contrast are typically associated with emotional processing, but a number are considered important for episodic retrieval. One notable finding was that right PFC was more strongly activated during the emotion task instruction period, and left PFC during the people task instruction period. Given the heterogeneity of PFC and the fact that the areas revealed in this contrast did not overlap with areas from other contrasts preclude making strong conclusions about the significance of this finding, but similar areas have been proposed to index control processes during source memory tasks (Dobbins et al, 2002), consistent with the findings presented here. Additionally a region of left inferior parietal cortex, which overlapped with regions discriminating source hits from correct rejections, was more strongly engaged in the emotion block instruction period. This regions has been proposed to index successful recollection, and also showed

enhanced activity during performance of the emotion task. Additional to these parietal findings, one of the areas identified in the contrast between emotion and people discrimination tasks was the hippocampus, another region strongly associated with episodic memory. These effects together suggest facilitated retrieval activity during emotion discrimination. One possibility is that successful performance on the emotion task required a greater amount of information to be retrieved from memory than did the people task, although there was no direct evidence for this. If this were the case then one would predict that, at similar levels of performance, hippocampal and parietal activity would be increased during performance on the emotion task. Alternatively, when behavioural responses are contingent upon retrieval of emotional information, rather than other aspects of a memory trace, it may be that greater resources are dedicated to episodic retrieval due to the importance of the contingent response. These effects on memory processing regions may reflect decreased firing thresholds or enhanced external input to these areas as a result of tonic top-down influences, initiated during the instruction period.

Other task effects were seen in areas of caudate and thalamus, which were identified in the contrast of source hits in all conditions with correct rejections. Effects were also seen in anterior insula which in the previous experiment (chapter 7) showed enhanced activity for source hit trials. It has been previously suggested that the activation of these areas, in addition to those more typically associated with retrieval of source memory might reflect task requirements to specifically retrieve information about the emotional nature of a previous experience, or to make an emotional judgment based upon retrieved information. The presence of these effects during the task but not the instruction period is more supportive of post-retrieval facilitation, although some material specific retrieval strategies might only be engaged on a trial

by trial basis. The present design does not allow unequivocal dissociation of these possibilities because of cueing tasks on a blocked, rather than trial-by-trial basis.

Other effects occurred in areas associated specifically in emotional processing, and identified in this and previous experiments to be involved with retrieval of emotional but not neutral memories, were also more active during the emotion discrimination task. These areas included both amygdalae, medial orbitofrontal cortex, VMPFC, and other frontal regions. One parsimonious explanation for these effects is that the areas engaged during emotional retrieval are more strongly activated when that emotional information is relevant to the current situation. This is particularly probable for those areas engaged more strongly both for the emotion discrimination task and, in both tasks, for items previously associated with negative contexts. This includes effects in left amygdala, PFC and posterior cingulate.

Some of the task effects might reflect tonic engagement of emotion-sensitive areas during emotion discrimination, though such effects were not revealed during the pre-block instruction periods. One theory of mood congruency effects on memory retrieval suggests that the enhanced memory for emotional stimuli when a subject is in an emotional state of the same valence may be supported by engagement of the same emotion sensitive structures or 'nodes' during both encoding and retrieval (see Lewis and Critchley, 2003). As has been discussed previously, different components of a memory trace may be stored in specific sensory and emotion sensitive brain regions, bound together by memory processing areas, particularly the hippocampus. If part of the memory trace is active, the chance of retrieving the other associated elements is improved, such that engagement of structures sensitive to negative emotions is likely to improve the chance of retrieving negatively valenced memories. It is possible that during the emotion task, tonic engagement of emotion sensitive structures could

improve the retrieval of emotional memories aiding the discrimination task. However, this might also impair retrieval of neutrally valenced memories, presumably impairing task performance on these trials.

Another alternative possibility is that some of the task effects reflect emotional control processes. In particular, the orbitofrontal cortex (Bechara, 2004) and VMPFC (Drevets and Raichle, 1998) have been associated with emotionally guided decision making and control of emotional processing (see also Phan et al, 2004). The preferential engagement of these areas when the task requires emotional discrimination may reflect the relative priority of retrieved information in guiding behaviour.

Dynamic Causal Modelling

The DCM analysis firstly revealed that the haemodynamic activity associated with retrieval of emotional and neutral memories could be well modelled by a network consisting of the amygdala, hippocampus and OFC, together with visual fusiform cortex. The functional connectivity from fusiform to hippocampus was slightly, but significantly, greater for emotional than neutral source hits, suggesting that these trials were associated with facilitated retrieval of information from episodic memory. Given that both these trial types were associated with successful source memory, the differences are likely to reflect differences in the amount or vividness of information recollected.

Emotional source hits were also associated with increased connectivity from hippocampus to amygdala. This suggests that amygdala activation reflects a reaction to episodic retrieval of emotional information, mediated by the hippocampus. This

finding is consistent with the post-retrieval timing of the major emotion effects observed in the earlier ERP experiments, although those effects are unlikely to reflect amygdala activity directly. Episodic retrieval of emotional memories is associated with both enhanced retrieval processing and engagement of emotion specific processing in reaction to retrieved information.

The model also revealed significant effects of the retrieval task on neural interactions. When subjects performed the emotion discrimination task connectivity between amygdala and hippocampus was increased bi-directionally. The increased influence of hippocampus on amygdala activity may reflect potentiated or more sustained engagement of the amygdala when emotional information is retrieved. The influence of amygdala on hippocampus during the emotion discrimination task is less clear, but might reflect ongoing facilitation of retrieval processing, tonic activation supporting retrieval of emotionally valenced memory (see mood congruency discussion above), or possibly re-encoding of emotional information.

The emotion discrimination task also acted to engage OFC, which thus in turn had increased influence on amygdala and hippocampus. As has been discussed previously (chapter 2), OFC is associated with higher order representation of the affective value of stimuli (Rolls and Kringlebach, 2004) and emotionally guided decision making (Bechara, 2004). The present findings suggest an important role of OFC in modulating emotional (and, in this case, mnemonic) processing according to the current behavioural context. OFC may act as an interface between systems underlying emotional and non-emotional cognitive processing. The pattern of abnormal behaviour in patients with damage to the OFC, whereby acquired emotional knowledge is not applied to behavioural selection, with particular deficits in inhibition of socially inappropriate, motivationally driven behaviour (Bechara, 2004; Blair,

2001; Damasio et al, 1994; Krawczyk, 2002), is consistent with the role suggested for OFC here.

Summary

The present findings reveal firstly that a number of the effects observed during retrieval of emotional and non-emotional information can be modelled effectively in terms of a simple model incorporating bottom-up and top-down inputs into a network of interacting brain regions. Retrieval of source memory about emotional contexts is associated with an enhanced influence of the hippocampus on the amygdala, regardless of whether emotional information is task-relevant. However, when emotion is task relevant hippocampal-amygdala interactivity is increased bi-directionally, likely facilitating both the retrieval of emotional information, and appropriate emotional response to that information, as well as possibly having effects on re-encoding/consolidation. The OFC is also engaged, and enhances activity in hippocampus and amygdala, during the emotion task, consistent with a proposed role in executive control of emotional processing. The findings also revealed other effects reflecting the type of information to be retrieved from episodic memory, some of which preceded retrieval processing, and may reflect engagement of specific retrieval strategies or orientations.

General Discussion

This section aims to bring together the findings from the experiments described in this thesis, and consider the implications of the findings for the understanding of emotional memory. This begins with brief summaries of each of the experiments carried out, describing the purpose and main findings of each. While some of the issues raised by the results are specific to particular experiments, others have a more general relevance and will be revisited in light of the other findings. Finally, some outstanding issues and directions for future research will be discussed.

Experiment Summaries

Experiment 1: Event-Related Potential Correlates of the Incidental Retrieval of Emotional Context

Scalp-recorded ERPs were used to investigate neural activity elicited by recognition of pre-experimentally neutral item pictures encoded in either positively, negatively or neutrally valenced photographic contexts. Behaviourally, there was a small but significant recognition advantage for items encoded in positive contexts compared to either neutral or negative contexts. ERPs elicited by correctly recognised items encoded in neutral contexts (neutral hits) were distinguished from those elicited by items correctly judged to be new (correct rejections) by a positivity maximal over left parietal scalp, onsetting around 500ms post-stimulus. This left parietal old/new effect has previously been taken to reflect a neural correlate of recollection. The ERPs elicited by negative and positive hits did not differ from one another, but did differ from those associated with neutral hits. The most notable emotion effect was a large positive shift, greatest over left temporal and frontal scalp, onsetting 200-300ms after

the onset of the left parietal old/new effect. Additionally, small but significant differences were found between emotional and neutral hits early in the epoch, which were not fully characterised until experiment 4.

The late-onsetting emotion effects were topographically dissociable from neutral old/new effects, implying engagement of qualitatively different cognitive processes during recognition of items encoded in emotional vs. neutral contexts. That these differences arose primarily subsequent to the left parietal effect suggests that they may reflect differences in the post-retrieval processing of incidentally retrieved contextual information as a function of its emotional content.

Experiment 2: Event-Related Potential Correlates of the Incidental Retrieval of Emotional Context II: Controlling for novelty and interest effects

Scalp recorded ERPs were used to investigate neural activity during a recognition test, similar to that used in experiment 1, except that neutral contexts were divided into two groups. One group of neutral contexts consisted of photographs depicting novel and interesting scenes which were not repeated during the experiment, and a second group of less interesting photographs, which were used as contexts in association with multiple items at encoding, to decrease their novelty. Consistent with the findings from the first experiment, items encoded in association with positive contexts were more likely to be recognised than those from any other contexts. ERPs did not reveal any significant differences in the waveforms associated with the two different neutral categories. Similar to experiment 1, ERPs for emotional hits (collapsed across positive and negative) were more positive going that those for either category of neutral hits, with primary emotion effects onsetting subsequent to the left parietal

old/new effect and being focussed over left fronto-temporal scalp. These findings reinforced the findings of experiment one, and suggested that the modulation of processing for items previously associated with emotional contexts could not be solely attributed to factors of interest or novelty.

Experiment 3: fMRI correlates of the incidental retrieval of emotional context

Neural activity was measured using fMRI during performance of a recognition memory task for items encoded in positively, negatively and neutrally valenced contexts, similar to experiment 1. Consistent with findings from the earlier experiments, items associated with positive contexts were more likely to receive a correct recognition judgment than their counterparts from negative or neutral contexts. The majority of differences in the haemodynamic correlates of recognising items from emotional and neutral contexts were common to both negative and positive conditions. These valence-independent emotion effects reflected firstly enhanced activity in structures which appeared to be involved in retrieval of items from neutral contexts, specifically in angular gyrus and middle temporal gyrus. In addition to this enhancement of 'generic' retrieval processing, there was engagement of a number of emotion-sensitive brain regions, including left amygdala, insula, OFC and VMPFC. These findings were consistent with the view that emotional retrieval engages processes which are partially qualitatively distinct from those involved in retrieval of neutral information. Additionally, a region of left amygdala overlapping that revealed during emotional retrieval had also shown enhanced activity during encoding of emotional retrieval, suggesting that retrieval of emotional information may involve recapitulation of processes engaged during its encoding.

Experiment 4: Event-Related Potential Correlates of the Successful and Unsuccessful Retrieval of Emotional Context

ERPs were used to examine firstly whether the previously described ERP emotion effects would be ameliorated when neutral contexts were made more behaviourally significant by making source information relevant to the memory task. The experiment also examined whether emotion effects would be modulated according to whether there was successful retrieval of contextual information or not, and the behavioural effects of emotional context on source as well as item memory. As in the previous experiments, items from positive contexts were more likely to be recognised than those from neutral or negative contexts, but recognised items were equally likely to receive an accurate source judgment if they had been paired with positive or negative contexts at study, with items from neutral contexts attracting fewer accurate source judgments. Separating emotional contexts according to how emotional they were judged to be by individual subjects revealed that increasing the valence of positive contexts linearly enhanced both recognition and source accuracy, while for negative contexts the most extreme contexts were associated with the greatest source accuracy, but lower recognition accuracy than for more moderately negative contexts. This suggested that either the most extreme negative contexts detracted from the encoding of their associated neutral objects (but were well remembered on occasions when the item was recognised) or that emotion effects on memory performance may be constituted of both valence-specific effects on recognition and valence-independent effects (possibly mediated via arousal alone) on source memory. ERPs revealed the presence of emotion effects both in comparisons of emotional vs. neutral source hits and source misses, but source accuracy did modulate the form of these emotion

effects. For source hits, emotion effects were qualitatively similar to those seen in experiments 1 and 2, with a late-onsetting positivity over left fronto-temporal scalp, while source miss emotion effects were predominantly over right frontal areas. The results suggest that differences in the retrieval processing of neutral items encoded in emotional or neutral contexts may arise from at least two distinct mechanisms – firstly modification of the value of the items themselves, and secondly activity arising from processing the retrieved emotional context, with different consequences for retrieval processing. Data from this experiment was also combined with that from experiment 1 to better characterise early emotion effects, prior to the onset of the left parietal effect. This analysis revealed small but significant effects over lateral temporal scalp prior to the left parietal effect, and thus presumably recollection. This supported the above view that recollection of emotional contexts was not necessary in order to observe emotion related differences in this paradigm, though successful recollection was associated with considerable additional modulation of post-retrieval activity.

Experiment 5: fMRI Correlates of the Intentional Retrieval of Emotional Context

This experiment used fMRI and a design similar to that employed in experiment 4 to determine the brain regions underlying emotional modulation of source hit and source miss processing. As in previous experiments, items from positive contexts were more likely to be recognized than were other old items, but in this experiment there was also a small recognition advantage for items encoded in negative vs. neutral contexts. As in experiment 4, both positive and negative contexts were associated with improved source accuracy. fMRI revealed distinct patterns of emotion related activation for contrasts of source hit and source miss trials. An interaction of context

valence and source accuracy revealed that processing distinguishing emotional and neutral source hits activated a primarily left-lateralised network including left amygdala, anterior insula, and VMPFC. In contrast, emotional source misses were associated with activity in right amygdala, PFC and extrastriate visual areas. The findings suggested firstly that left and right amygdala might have differing roles in emotional memory processing, with right amygdala indexing general arousal (under the assumption that items encoded with emotional contexts acquired some of their value by association) and left amygdala decoding stimulus-specific emotional information. If emotional material is successfully retrieved from memory then it may be represented internally, driving a cascade of emotion processing in order to address current behavioural requirements. Alternatively, if an item is 'tagged' as having significance, but the information retrieved from memory about that item is insufficient to make an accurate response, then the circuit engaged may help to analyse the cue object and iteratively drive further retrieval attempts.

Experiment 6: Neural interactions underlying retrieval of emotional memory

This experiment used fMRI and dynamic causal modelling in order to examine whether the neural activity observed in previous experiments could be explained in terms of interactions between brain regions subserving emotional and mnemonic processing, and to test whether behavioural context could modify these effects. Neutral items were encoded with contexts which were either neutral and contained people, neutral without people, negative with people or negative without people. At test, two alternating source tasks required judgments to be made either as to the valence of the context associated with each item, or whether it had contained people. Behaviourally, items were more likely both to be recognised and attract accurate

source judgments if they had been associated with negative contexts or contexts containing people. The effect of the presence or absence of people may reflect a difficulty confound, as subjects made associations more rapidly at encoding for contexts containing people. However, there was no difference in the difficulty of encoding task between negative and neutral contexts. Independent of the source task, negative source hits were associated with enhanced activity in a network including left amygdala, and a number of other areas highlighted in previous experiments, although there were no significant effects in the regions of OFC and VMPFC previously revealed. However, comparing activity during performance of the emotion discrimination task revealed a large network showed enhanced activity, including bilateral amygdala and OFC, and left VMPFC and hippocampus, suggesting that when retrieval of emotional information is important for meeting current response requirements that there is engagement of emotion-sensitive and mnemonic structures in order to support this. We identified a network of amygdala, hippocampus and medial OFC within which the observed effects could be well modelled using DCM. This revealed that source hit responses to items associated with negative contexts increased connectivity from visual areas to hippocampus, and from hippocampus to amygdala, independent of task effects. When emotion was task-relevant connectivity between amygdala and hippocampus increased bi-directionally, and there was additional engagement of OFC, which thus exhibited increased influence upon amygdala and hippocampus. The findings suggested both that integration of structures subserving affective and mnemonic processing underlies successful retrieval of, and response to, emotional memories, and that top-down control mechanisms act to optimise this integration when such information is relevant to ongoing behaviour.

Implications and Outstanding Issues

In all of the experiments described in this thesis there was evidence for distinct patterns of neural activity associated with retrieval of emotional and neutral memories. Additionally, there was evidence of enhanced memory for items encoded in emotional contexts. Recognition memory was consistently enhanced for items encoded in association with positive contexts compared to either negative or neutral contexts. The degree of enhancement was correlated with subjective ratings of valence. In contrast, items associated with negative contexts showed an inconsistent improvement in recognition performance relative to those from neutral contexts. There are several possible reasons for the different potency of positive and negative emotion in enhancing recognition memory. Clearly there is no simple correlation with absolute valence or arousal, as negative contexts were on average more strongly valenced and more arousing than were positive contexts. However, it may be that the most extreme negative backgrounds actually impaired the encoding of objects associated with them, as a result of diverting excessive attention towards the context at the expense of the concurrently presented object. This interpretation is consistent with findings supporting an 'inverted U' model mapping degree of emotional arousal against effect on task performance (Strange et al, 2003; Richter-Levin, 2004). In the present results there was some indication that items encoded with extremely negative contexts were less likely to be recognised than were those encoded with moderately negative contexts, in contrast to the linear relationship observed for positive contexts. The results of the present experiments however did not provide any conclusive evidence for such a relationship, perhaps because of a lack of resolution of the ratings scales used, or inter-subject variability in their use. In order to investigate this further

in future, objective measures of arousal, such as GSR, could be correlated with recognition performance.

There are other possible reasons for differing effects of positive and negative emotion on recognition memory performance. Given the equivalent effects of positive and negative contexts on source memory performance, it may be that only positive emotion modulates familiarity processing, while both positive and negative emotion modulate recollection. Alternatively, it may be that positive emotion facilitates binding of disparate elements of an episode, while negative emotion facilitates only memory for the emotional stimulus itself (see Erk, 2003). These possibilities could be investigated by encoding positive and neutral objects together with neutral contexts about which source judgments could be made. If positive objects were more likely to be recognised than negative, but source memory was equivalent, it would suggest a specific effect of positive emotion on familiarity processing. In contrast, if recognition performance was equivalent in the two conditions, but source accuracy improved for contexts associated with positive test items, this would suggest different effects on binding episodic elements together. In either scenario, the influences of positive and negative emotion on memory processing may be mediated by different combinations of neurotransmitters, with effects of positive emotion principally mediated through increased dopamine release (see Ashby et al, 1999), with negative emotion being principally adrenergic (see Cahill, 1999). This question of whether positive and negative emotion modulate memory processing in qualitatively different ways, or whether differences in processing can be accounted for in terms of absolute valence and arousal, is important in understanding mechanisms of emotional memory, and for the design of experiments investigating them. Certainly the existence of mood congruency effects on memory performance implies some valence-specific aspects of

memory modulation (see Lewis and Critchley, 2003), but it is not clear whether such effects reflect match/mismatch of encoding and retrieval conditions, or a graded effect whereby in a negative context the most negatively valenced items would be best remembered and the most positively valenced would pay the greatest performance penalty. Experiments using carefully balanced and diverse emotional stimuli, subject-specific behavioural and physiological indices of valence and arousal, and a variety of mood manipulation methods may be able to address this issue. Additionally, it is of interest to examine the neurochemical basis of positive and negative emotional modulations of memory, particularly at the time of retrieval, in contrast to earlier experiments, which have focussed primarily on negative emotion, the adrenergic system and encoding processes (e.g. Cahill et al, 1994; Cahill and Alkire, 2003; Strange et al, 2003).

In addition to the effects on behaviour, the experiments in this thesis provided consistent evidence for engagement of different neural populations, and cognitive processes, during recognition of items previously encoded in emotional and neutral contexts. The first important issue to consider is exactly what processes are investigated using a contextual paradigm, as in the present thesis, rather than memory for emotional stimuli *per se*. Recognition of emotional stimuli will be associated with neural activity reflecting both processing of the stimuli themselves and emotional retrieval processing, reflecting modulation of familiarity, recollection or both. Although paradigms examining recognition of emotional stimuli may parallel many real life situations, it is difficult with such designs to unequivocally determine the effects of emotion on retrieval (see chapter 2 for extended discussion). Paradigms examining free recall of emotional material avoid confounding effects of mnemonic and online processing, but do not allow event-related designs to be utilised during

retrieval, such that state and item-related effects of emotion cannot be easily dissociated. Paradigms examining activity associated with retrieval of neutral items encoded in differently valenced contexts investigate a rather specific form of emotional memory, but avoid some of the confounding issues raised above. Differences in activity associated with items encoded in emotional and neutral contexts may have arisen from by at least two separate mechanisms. Firstly, the emotional value of items may be modified by past experience, such that items associated with emotional contexts acquire emotional significance. Therefore, some differences in processing may arise from implicit memory effects, not dependent on retrieval of the relationship between context and object. Such effects may have some commonalities with responses to conditioned stimuli. Additionally, recognition of objects may be accompanied by recollection of the associated contexts. Emotion effects arising from recollection would be expected to be similar to those underlying free recall of emotional information, although free recall is likely to involve some additional processing (see chapter 1).

The present experiments reveal effects of emotion on retrieval processing whether or not there is an explicit requirement for retrieval of emotional information, suggesting that emotional episodes may be automatically and involuntarily retrieved in response to associated cues. These emotion effects do not appear to be explained by differences in the novelty or interest of the encoding contexts, nor by the difficulty of the encoding task. ERP effects indicated that emotion modulated processing both prior and subsequent to recollection, as indexed by the left parietal old/new effect. Prior to recollection, emotion effects took the form of a small positive shift over lateral temporal scalp. These effects are likely to reflect differences in processing items with acquired emotional value and those which are neutral. Subsequent to

recollection, emotion effects differed according to whether information about contexts was successfully retrieved. Recollection of emotional contexts elicited a left fronto-temporal positivity, assumed to reflect differences in the processing of retrieved emotional and neutral information. In contrast, when attempted retrieval of contextual information was unsuccessful, the late emotion effects had a right frontal distribution, and may reflect modulation of processing iteratively driving further attempts at recollection in order to complete the source memory task successfully.

The fMRI results revealed effects of emotion both in brain regions supporting retrieval of neutral memories, and in a network of emotion-sensitive structures. Due to the temporal resolution of this technique, we cannot determine which fMRI effects precede recollection and which follow it, but there will be some discussion of which effects might reflect early processing of items from emotional and neutral contexts, and which are contingent on retrieval of emotional contexts. Effects dependent on source retrieval were revealed by interactions between emotion and source memory, described in chapter 7. Successful retrieval of emotional contexts engages a primarily left-lateralised network including amygdala, insula and VMPFC, all regions implicated in different aspects of emotional processing. VMPFC, together with mOFC, has been implicated in the control of emotion, and emotionally guided decision making (see chapters 2, 8). Effects in this brain region are likely to reflect post-retrieval evaluation of emotional retrieval products, and selection of appropriate behavioural responses. This view is supported by the increased activity in VMPFC when emotion is task relevant than when it is not, and by the late onset of left fronto-temporal ERP effects, to which activity in this region may be a contributor.

The anterior insula, a region sensitive to internal state signals, such as pain, and previously associated with retrieval of emotion, was engaged by successful retrieval

of both neutral and emotional contexts when the emotional status of those contexts was relevant to current behaviour. This insula region was also more strongly engaged when the retrieved information was emotional than when it was not. The dependence of insula activation on both successful retrieval and the task-relevance of emotional discrimination suggests a possible role in supporting the internal representation of retrieved contexts, or the emotional elements of them, in order to allow emotion discrimination, probably subserved by regions of prefrontal cortex (see above). This processing may then be enhanced when the retrieved information is emotional. The involvement of the anterior insula in internal representation of emotion is in keeping both with findings from emotional induction, where processing of internally generated emotion activates insula to a greater extent than processing of external emotion or internally generated neutral material, and with its role in responding to other behaviourally significant interoceptive information.

The effects observed in the amygdala were amongst the most interesting in the work described. This brain region is one of those most strongly associated with emotional processing, and particularly with modulating the encoding of emotional stimuli and episodes. The present findings, together with some other supporting results discussed in chapter 5, lend credence to the view that this structure may also be important in the retrieval of emotional episodes. Evidence was found for dissociable roles of left and right amygdala in modulating emotional processing, discussed in depth in chapter 7. Certainly left amygdala activity was found to be consistently engaged by successful retrieval of emotional contexts, whether or not they were relevant to ongoing behaviour (though was more strongly engaged during task-relevant emotional retrieval), and has been reported in a number of other studies involving retrieval of emotional information, directly or indirectly (see chapter 2). One difficulty in making

strong conclusions about the role of the amygdala is the lack of timing information – the insensitivity of ERPs to activity in this region due to its closed field configuration means we have little guide as to whether amygdala is engaged prior to, concurrent with, or subsequent to recollection. A post-retrieval locus for amygdala effects would be consistent with the timing of the major ERP emotion effects, which may result indirectly from amygdala, as a result of amygdala-cortical interactions. A plausible explanation for such an effect would be that amygdala responds to internally represented emotional information much as it does to that sensed externally, possibly having a role in decoding its significance. An equally plausible alternative is that amygdala may be activated as part of the retrieval process itself. As discussed earlier, one model of associative memory considers memory traces to be distributed across the brain regions supporting the processing of specific features of a stimulus during encoding, with the hippocampus acting as an 'index' connecting these elements into a coherent engram. Within this model, the amygdala may store the representation of emotional aspects of a retrieved trace, while visual regions support its perceptual aspects. The two possibilities above are difficult to distinguish experimentally – the engagement of overlapping regions of left amygdala during encoding and retrieval of emotional contexts could be attributed either to recapitulation of encoding activity or similar responses to the external and internal representation of emotion; the timing of late-onsetting ERP effects just subsequent to recollection might indirectly reflect amygdala effects either concurrent with or just after left parietal old/new effects. Both proposals would also be consistent with the unidirectional influence of hippocampus on amygdala during emotional retrieval in the DCM. As the emotional impact of unique encoded stimuli and the recollected memories of those stimuli are likely to be highly correlated it is not trivial to separate these two possibilities by, for

example, comparing the correlation of amygdala activity with arousal ratings or GSR at encoding and retrieval, though such methods could be tried. Alternatively an experiment similar to those described in this experiment could be carried out using patients with electrodes implanted in MTL, possibly allowing the relative timing of amygdala and hippocampal activity to be determined. It is also possible, though less likely, that left amygdala is engaged prior to recollection of emotional episodes. In this scenario, items previously associated with emotional contexts engage the amygdala which then facilitates retrieval of the associated emotional episode. However, given the timing of the major emotion effects in the ERP experiments, and the directionality of effects in the DCM, such a scenario is less plausible than engagement of the amygdala concurrent with or subsequent to recollection.

The right amygdala appears to play a qualitatively different role to that discussed above for the left amygdala. Right amygdala was engaged preferentially for emotional source miss trials in experiment 5, and was more active during the emotional discrimination task in experiment 6. Various proposals of different roles for left and right amygdala are discussed at length in chapter 7 and these arguments are not reiterated here. The present findings were insufficient to allow unequivocal dissociation of two previous proposals, one supporting a specialised role for left amygdala in conscious processing and decoding of the emotional significance of emotional stimuli, with right amygdala indexing arousal whether or not stimuli are consciously perceived as stimuli (Gläscher and Adolphs, 2003) compared to an account of left amygdala specialised for verbally, and right for non-verbally conveyed emotional information (Funayama et al, 2001). It would certainly be of interest to test these possibilities using both verbal and non-verbal emotional material and modulating levels of awareness within a single experiment, and to employ such a

paradigm both in patients with unilateral amygdala damage and normal subjects in an imaging experiment. Any relation of the present findings to a general distinction between left and right amygdala in emotional processing is dependent on the assumption that retrieved emotional episodes produce similar emotional modulations, at least in the amygdala, to perceived external emotional stimuli. Although the findings of partially overlapping activity during encoding and retrieval of emotional episodes, including effects in left amygdala, would support this idea, it is possible that the predominance of left vs. right amygdala in the present findings reflect a specialised role for left amygdala in processing internally represented emotion (see chapter 7 for further discussion).

Regardless of the potential lateralisation of amygdala function, either in general emotional processing or specifically modulation of memory, one major outstanding question is whether or not the amygdala is necessary for the normal retrieval of emotional memories. This issue is not trivial to address – clearly patients with amygdala damage can still retrieve information about emotional events, but whether there are qualitative differences in the retrieval or post-retrieval processing is not yet clear. There is some emerging evidence that amygdala lesions may reduce the strength of affective responses, and the emotionality of descriptions of emotional events occurring prior to amygdala damage (T. Buchanan, personal communication), implying perhaps that either the emotional aspects of the event are not retrieved (for example, one might remember being in a car crash, but not the feelings of fear during the event) or that the response to retrieved emotional information is blunted. However, further work is required in this area, taking care to balance non-emotional factors such as age and vividness of memory and examining the potentially subtle changes in behaviour arising from abnormal emotional modulation of retrieval.

In addition to right amygdala, a number of other brain regions were sensitive to emotional manipulation in the absence of contextual recollection. The majority of these effects are likely to occur after an initial recollection attempt, given the timing of ERP source miss effects. In particular, right frontal regions were revealed in the fMRI source miss effects, while the ERP effects were similar in distribution to right frontal effects taken to reflect post-retrieval monitoring processes (Wilding and Rugg, 2000). These postretrieval processes have been proposed to monitor whether retrieved information is sufficient to support response requirements, and drive further retrieval attempts if it is not sufficient (Shallice and Burgess, 1996). Activity in right DLPFC has been reported in contrasts of K vs. R judgments in an R/K paradigm (Henson et al, 1999) and items recognised at low vs. high confidence in a recognition memory task (Henson et al, 2000), consistent with the role proposed above. It is plausible that the emotion effects associated with source miss trials, described in chapters 6 and 7, is that items previously associated with emotional contexts are either more likely to be subject to postretrieval monitoring, or engage these processes more strongly. It may be the case that even when context-item associations are not explicitly retrieved, that items from emotional contexts are still tagged as 'significant' in some way, which may enhance the resources dedicated to their processing, including post-retrieval monitoring. An alternative explanation relates to the possibility that monitoring processes may only be strongly engaged and drive further retrieval attempts when the 'strength' of retrieved information is close to a response threshold – this is consistent with the confidence data discussed above, low confidence responses presumably being those closest to discrimination boundaries. If this is the case then it may be that more items from emotional contexts are close to the response threshold, as a result of the enhancement in source memory for these

contexts, and thus are subject to right frontal monitoring processes. A similar enhancement of memory increasing the proportion of items close to response threshold has been proposed to underlie enhanced right frontal effects in a mood congruency paradigm (P.A. Lewis, H.D. Critchley, A.P.R. Smith, R.J. Dolan, in prep). In any case, the emotion effects observed in the source memory experiments were clearly modulated by an awareness of context-object relationships, but emotion still has multiple influences on processing in the absence of such awareness.

While most of the work described in this thesis was concerned with determining functional dissociation and specialisation of neural processing for emotional and neutral memory retrieval, also investigated was the functional integration between different brain regions, and how this was modulated by item history and experimental context. One physiologically and anatomically plausible network of structures was investigated, and did indeed show context-dependent effects on effective connectivity. However, the model used was rather restricted, and it would of interest in future to expand investigation to a wider range of neural regions highlighted in the standard SPM contrasts. It would also be worthwhile to examine identical networks during encoding and retrieval of emotional memory – although there is imaging evidence for amygdala-hippocampal interactions during encoding (Dolcos et al, 2004; Richardson et al, 2004) the relationships identified have been static and restricted to these two regions alone. Using identical models at encoding and retrieval would allow further investigation of models predicting recapitulation of encoding activity at retrieval, and whether such models explain storage of the emotional aspects of a memory trace. One might also predict that the directionality of certain influences would be reversed during encoding and retrieval, for example that encoding of emotion would involve a

stronger influence of amygdala on hippocampus, in contrast to the results in chapter 8 showing hippocampus influencing amygdala during emotional retrieval.

One issue of interest relates to the finding of few valence-specific emotion effects, with most emotion effects being equivalent for positive and negative valences. This is perhaps somewhat surprising given the differences in appropriate behavioural responses to positive and negative stimuli (in real life), the likelihood that positive and negative emotion are mediated by partly dissociable neurotransmitter systems and the proposed specialisation of some neural structures for processing specific basic emotions, such as fear or disgust (e.g. Calder 2000). There are four reasonable explanations for the findings presented in the present thesis. The first is that there are fewer differences between the processing of negative and positive emotion than previously believed if positive and negative stimuli are well balanced in terms of absolute valence and arousal – certainly the amygdala, which was long thought to be specialised for negative emotion, particularly fear, is sensitive to arousing positive stimuli as well (Garavan et al, 2003; Hamman et al, 2001). While our stimuli were not perfectly balanced, with negative stimuli being on average slightly more arousing, the differences between these factors were relatively small. Therefore perhaps our rather limited valence-specific effects reflect the only true differences in the processing of positive and negative emotion. A second possibility is that the apparent similarities reflect a lack of resolution in non-invasive techniques. It may be the case that, for example, the amygdala processes both positive and negative emotional stimuli but different sub-populations within its nuclei are valence-specific. Issues such as this can only be resolved with invasive recording from individual neural populations. A third possibility is that valence is a poorly chosen dimension on which to organise emotions. It may be that some processing is common to all emotions, and

other processing is specific not to a particular valence, but to specific emotions such as fear, anger, happiness, disgust etc. It would be of interest in future to develop a well balanced stimulus set incorporating equivalent stimuli inducing each of the basic emotions and examine emotion-specific differences, common emotion effects and assess the value of valence and approach/withdrawal dimensions for explaining the neural activity observed in such an experiment. Finally, it may be that the findings reflect a modified emotional response to retrieved emotional information, with valence-specific differences blunted, perhaps because decision making based on past experience is more cognitive than rapid reflexive responses to imminent danger or reward, with previously reported valence effects primarily reflecting reflexive responses.

Conclusions

The present experiments have both helped to delineate the processes involved in retrieving emotional episodes from memory, and set out a framework for further investigation using a paradigm which does not confound mnemonic modulation with on-line processing of emotion. Enhanced memory for emotional material is accompanied by modulation of mnemonic processing and engagement of a number of emotion-sensitive structures, these brain regions interacting to support emotional retrieval and subsequent guidance of behaviour. A number of future directions have been proposed, including examining the neurochemistry of positive and negative emotion effects on memory, careful delineation of the roles of left and right amygdala in emotional processing, commonalities and differences in the processing of different emotions and characterisation of wider networks of affective and mnemonic structures during both encoding and retrieval of emotional episodic memories.

Although there remain a number of outstanding issues in this field, this thesis reveals how emotional memories engage specialised cognitive processing, which may support our experiences of reliving past emotional experiences, and underlie their power to pervade our thoughts and actions.

Abbreviations

ACC = anterior cingulate cortex

AIC = Akaike's information criterion

ANOVA = analysis of variance

AP = anterior-posterior position

BA = Brodmann area

BIC = Bayesian information criterion

BOLD = blood oxygenation level dependent

CER = conditioned emotional response

CS = conditioned stimulus

DCM = dynamic causal modelling

DLPFC = dorsolateral prefrontal cortex

EEG = electroencephalography

EM = expectation maximisation

EOG = electro-oculogram

ERP = event-related potential

EPI = echo-planar imaging

FWHM = full width half maximum

GLM = general linear model

GSR = galvanic skin response

HRF = haemodynamic response function

HM = hemisphere

IAPS = International affective pictorial system

IT = item type

K = know

LPP = late positive potential

LT = lateral site

LTD = long-term depression

LTP = long-term potentiation

MNI = Montreal Neurological Institute

MRI = magnetic resonance imaging

fMRI = functional magnetic resonance imaging

efMRI = event-related functional magnetic resonance imaging

NMR = nuclear magnetic resonance

OFC = orbitofrontal cortex

PET = positron emission tomography

PFC = prefrontal cortex

PTA = post-traumatic amnesia

PTSD = post-traumatic stress disorder

R = remember

RT = reaction time

SCR = skin conductance response

SD = standard deviation

SNR = signal-to-noise ratio

SOA = stimulus onset asynchrony

SPM = statistical parametric mapping

ST = site

TE = echo time

TR = repetition time

US = unconditioned stimulus

VMPFC = ventromedial prefrontal cortex

Appendices

IAPS and other photographs employed as contexts, with pilot subject ratings

Contexts used for experiments 1,3,4 and 5. * Indicates non-IAPS photographs
Valence and arousal scale 1-5

IAPS Code	Description	Valence		Arousal	
		Mean	Variance	Mean	Variance
Neutral					
2190	Man	3.083	0.076	1.833	1.139
2200	Neut face	3.083	0.076	1.333	0.222
2210	Neut face	2.917	0.243	1.750	0.854
2214	Neut man	3.083	0.076	1.167	0.139
2215	Neut man	3.000	0.000	1.333	0.222
2220	Male face	2.833	0.306	2.167	0.972
2383	Secretary	3.000	0.000	1.167	0.139
2385	Girl	3.083	0.243	2.250	0.354
2440	Neut girl	3.000	0.333	1.500	0.417
2495	Man	3.000	0.167	1.500	0.583
2570	Man	3.083	0.243	1.667	0.722
2575	Propellor	3.083	0.076	1.667	0.722
2850	Tourist	3.250	0.188	1.750	0.354
2880	Shadow	3.167	0.306	1.583	0.410
2890	Twins	2.917	0.243	2.333	1.722
5395	Boat	2.917	0.410	2.167	0.639
5510	Mushroom	2.833	0.139	1.417	0.243
5533	Nature	2.833	0.306	1.917	0.743
5534	Nature	3.083	0.243	2.000	1.167
5535	Stilllife	3.083	0.076	2.000	1.333
6150	Outlet	3.000	0.000	1.500	0.917
6570.2	Blow dry	2.917	0.076	1.833	0.806
7000	Rolling pin	3.000	0.000	1.167	0.139
7002	Towel	3.083	0.076	1.333	0.389
7004	Spoon	3.000	0.000	1.000	0.000
7006	Bowl	3.000	0.000	1.250	0.688
7009	Mug	3.083	0.076	1.417	0.743
7010	Basket	3.000	0.000	1.167	0.139
7020	Fan	3.000	0.000	1.083	0.076
7025	Stool	3.000	0.000	1.000	0.000
7031	Shoes	2.917	0.076	1.417	0.576
7034	Hammer	3.000	0.000	1.417	0.243

7050	Hair dryer	3.000	0.000	1.250	0.688
7090	Book	3.000	0.000	1.583	0.743
7100	Fire hydrant	3.083	0.076	1.250	0.188
7130	Truck	3.083	0.076	1.750	0.521
7140	Bus	3.167	0.139	1.417	0.410
7150	Umbrella	3.000	0.000	1.083	0.076
7160	Fabric	3.167	0.139	2.250	1.188
7180	Neon building	2.917	0.076	1.667	0.389
7182	Checkerboard	3.000	0.167	2.833	0.972
7185	Abstract art	3.000	0.000	1.333	0.222
7186	Abstract art	3.083	0.076	1.667	0.889
7187	Abstract art	3.083	0.076	1.667	0.722
7217	Clothes rack	2.917	0.076	1.417	0.410
7233	Plate	3.000	0.000	1.333	0.389
7235	Chair	3.000	0.000	1.167	0.139
7491	Building	2.917	0.076	1.333	0.389
7500	Building	3.167	0.139	1.917	0.576
7550	Office	3.000	0.000	1.500	0.417
7595	Traffic	3.083	0.076	1.583	0.576
7640	Skyscraper	3.083	0.410	2.750	1.688
7705	Cabinet	2.917	0.076	1.333	0.222
7820	Agate	3.083	0.076	1.833	0.972
7830	Agate	3.083	0.076	2.000	0.500
7950	Tissue	3.083	0.076	1.167	0.139
9955*	Bridge	3.167	0.306	1.583	0.743
9956*	City	3.250	0.354	2.000	0.667
9961*	Truck	3.000	0.167	1.417	0.576
9965*	Snow trek	3.000	0.000	1.500	0.583

Negative

2205	Hospital	1.667	0.222	3.750	1.021
2352.2	Bloody kiss	1.083	0.076	4.583	0.243
2710	Drug addict	1.583	0.243	3.500	0.417
2800	Sad child	1.333	0.222	4.167	0.639
3010	Mutilation	1.000	0.000	4.333	0.222
3015	Accident	1.000	0.000	4.833	0.139
3030	Mutilation	1.583	0.243	3.417	0.243
3060	Mutilation	1.000	0.000	4.000	0.500
3062	Mutilation	1.000	0.000	4.667	0.389
3071	Mutilation	1.000	0.000	4.000	0.167
3080	Mutilation	1.000	0.000	4.500	0.583
3100	Burn victim	1.000	0.000	4.250	0.188

3102	Burn victim	1.000	0.000	4.667	0.222
3110	Burn victim	1.000	0.000	4.500	0.417
3120	Dead body	1.083	0.076	4.000	0.333
3168	Mutilation	1.000	0.000	4.833	0.139
3170	Baby tumour	1.000	0.000	4.667	0.222
3180	Battered female	1.333	0.222	3.833	0.306
3220	Hospital	1.833	0.139	3.083	0.910
3261	Tumour	1.083	0.076	4.417	0.243
3266	Injury	1.000	0.000	4.583	0.243
3400	Severed hand	1.167	0.306	4.000	2.000
3530	Attack	1.167	0.139	4.083	0.243
6213	Terrorist	1.667	0.222	3.167	1.472
6243	Aimed gun	1.500	0.250	3.250	0.688
6300	Knife	1.417	0.243	3.417	0.576
6312	Abduction	1.417	0.243	3.833	0.472
6313	Attack	1.083	0.076	4.250	0.188
6350	Attack	1.417	0.243	4.167	0.639
6510	Attack	1.250	0.188	3.750	0.521
6560	Attack	1.333	0.222	3.667	0.722
6570	Suicide	1.333	0.222	3.667	0.722
6571	Car theft	1.333	0.222	3.417	0.410
6821	Gang	1.667	0.222	3.417	1.410
7380	Cockroach pizza	1.833	0.139	2.417	0.743
9007	Needles	1.167	0.139	3.417	1.076
9040	Starving child	1.083	0.076	4.750	0.188
9050	Plane crash	1.083	0.076	3.833	0.806
9140	Cow	1.500	0.417	3.667	0.222
9181	Dead cows	1.083	0.076	3.333	0.889
9252	Dead body	1.000	0.000	4.667	0.222
9253	Mutilation	1.000	0.000	4.833	0.306
9265	Hung man	1.000	0.000	3.750	0.854
9300	Dirty	1.000	0.000	4.083	0.410
9320	Vomit	1.250	0.188	2.917	1.243
9400	Soldier	1.000	0.000	3.750	0.521
9405	Sliced hand	1.083	0.076	3.500	1.083
9410	Soldier	1.000	0.000	4.917	0.076
9415	Handicapped	1.833	0.139	3.250	1.188
9420	Soldier	1.000	0.000	4.417	0.410
9433	Dead man	1.250	0.188	3.833	0.639
9570	Dog	1.000	0.000	3.917	0.910
9571	Cat	1.250	0.188	3.333	1.389
9600	Ship	1.083	0.076	4.167	0.639
9800	Skinhead	1.333	0.222	3.750	0.188
9810	KKK rally	1.083	0.076	4.333	0.722

9910	Car accident	1.500	0.250	3.167	0.639
9911	Car accident	1.500	0.250	3.250	0.688
9920	Car accident	1.417	0.243	3.333	0.389
9921	Fire	1.417	0.410	3.500	1.750

Positive

1440	Seal	4.083	0.243	3.000	0.667
1460	Kitten	4.583	0.243	3.250	0.854
1610	Rabbit	4.083	0.243	2.333	0.556
1710	Puppies	4.500	0.250	2.917	0.910
1750	Bunnies	4.583	0.243	2.500	0.583
1920	Porpoise	4.333	0.222	2.917	1.076
2040	Baby	4.167	0.139	2.500	0.583
2091	Girls	4.417	0.243	2.583	0.743
2160	Father	4.000	0.167	2.167	0.806
2165	Father	4.167	0.306	2.500	0.750
2311	Mother	4.583	0.243	3.333	0.722
2340	Family	4.250	0.188	2.750	0.188
2352.1	Kiss	4.083	0.076	2.667	0.722
2360	Family	4.250	0.188	2.250	1.021
2530	Couple	4.167	0.139	1.917	0.910
2550	Couple	4.667	0.222	2.333	1.056
2660	Baby	4.417	0.243	2.500	0.417
4599	Romance	4.083	0.076	3.083	0.743
4603	Romance	4.083	0.076	2.250	1.188
4640	Romance	4.250	0.188	1.833	0.472
4641	Romance	4.000	0.167	2.333	0.722
5260	Waterfall	4.500	0.417	3.333	0.722
5270	Nature	4.333	0.222	3.750	0.854
5470	Astronaut	4.417	0.243	3.333	1.722
5480	Fireworks	4.250	0.188	3.500	1.250
5594	Sky	4.333	0.222	3.083	1.243
5600	Mountains	4.417	0.410	3.500	0.750
5621	Sky divers	4.167	0.472	3.083	1.243
5623	Windsurfers	4.417	0.243	3.417	0.910
5629	Hiker	4.333	0.222	4.083	0.910
5700	Mountains	4.583	0.243	3.833	1.972
5760	Nature	4.333	0.222	2.333	0.722
5780	Nature	4.083	0.243	3.083	0.576
5820	Mountains	4.167	0.306	3.000	1.500
5830	Sunset	4.583	0.243	3.333	1.389
5831	Seagulls	4.333	0.389	2.667	0.889

5910	Fireworks	4.500	0.250	3.333	1.056
7200	Brownie	4.000	0.000	2.667	0.722
7270	Ice cream	4.167	0.139	2.833	0.306
7280	Wines	4.000	0.000	2.250	1.188
7330	Ice cream	4.250	0.188	2.750	0.854
7470	Pancakes	4.333	0.222	2.250	0.854
8030	Skier	4.083	0.243	3.417	0.910
8170	Sailboat	4.000	0.167	3.250	2.688
8185	Sky divers	4.583	0.243	3.500	2.583
8190	Skier	4.417	0.243	3.917	1.076
8200	Water skier	4.000	0.167	2.750	0.688
8370	Rafting	4.167	0.139	3.167	0.806
8420	Tubing	4.000	0.000	2.000	0.500
8461	Happy teens	4.167	0.306	2.750	0.854
8496	Water slide	4.333	0.222	2.333	0.389
8497	Carnival ride	4.167	0.306	2.500	1.083
8500	Gold	4.167	0.139	3.000	1.000
8510	Sports car	4.083	0.243	2.833	0.806
8531	Sports car	4.250	0.354	2.917	0.910
9950	Temple	4.500	0.250	3.583	0.910
9951	Islands	4.667	0.222	3.583	0.410
9952	City	4.000	0.167	2.667	1.889
9958	Girl	4.167	0.139	2.333	0.722
9959	Penguins	4.333	0.222	2.750	0.521

Experiment 2 Contexts

Neutral Low Interest / Repeated

IAPS Code	Description	Valence		Arousal	
		Mean	Variance	Mean	Variance
2190	Man	3.083	0.076	1.833	1.139
5510	Mushroom	2.833	0.139	1.417	0.243
6150	Outlet	3.000	0.000	1.500	0.917
7090	Book	3.000	0.000	1.583	0.743
7217	Clothes rack	2.917	0.076	1.417	0.410
7705	Cabinet	2.917	0.076	1.333	0.222

Neutral High Interest

2206	Fingerprint	3.083	0.076	1.750	0.521
2383	Secretary	3.000	0.000	1.167	0.139

2514	Woman	3.083	0.076	1.750	0.354
2575	Propellor	3.083	0.076	1.667	0.722
2749	Smoking	3.083	0.076	1.417	0.410
2840	Chess	3.167	0.139	1.667	0.389
2850	Tourist	3.250	0.188	1.750	0.354
2870	Teenager	3.083	0.410	1.583	0.576
5455	Cockpit	3.000	0.000	1.500	0.417
7130	Truck	3.083	0.076	1.750	0.521
7140	Bus	3.167	0.139	1.417	0.410
7180	Neon building	2.917	0.076	1.667	0.389
7195	Teeth	3.250	0.354	2.750	1.688
7495	Store	3.000	0.167	1.583	0.576
7496	Street	3.250	0.354	1.583	0.576
7550	Office	3.000	0.000	1.500	0.417
7595	Traffic	3.083	0.076	1.583	0.576
7620	Jet	3.167	0.139	2.750	1.688
7640	Skyscraper	3.083	0.410	2.750	1.688
9700	Workers	3.167	0.139	1.583	0.576
9955*	Bridge	3.167	0.306	1.583	0.743
9956*	City	3.250	0.354	2.000	0.667
9961*	Truck	3.000	0.167	1.417	0.576
9965*	Snow trek	3.000	0.000	1.500	0.583
9980*	Tractor	3.167	0.306	1.417	0.410
9981*	Roadworks	2.917	0.076	1.667	0.389
9982*	Working	3.083	0.076	1.750	0.521
9983*	Street	3.167	0.139	1.417	0.410
9984*	Snow	2.917	0.076	1.667	0.389
9985*	Boat	3.083	0.076	1.583	0.576
9986*	Camp	3.167	0.139	1.417	0.410
9987*	Truck	3.250	0.354	2.000	0.667
9988*	Snow	3.000	0.167	1.417	0.576
9990*	Dock	3.000	0.000	2.000	0.667
9991*	Foggy	3.083	0.076	1.417	0.410
9992*	Bikes	3.167	0.306	1.667	0.389
9993*	Café	3.083	0.410	1.583	0.576
9994*	Ticket office	3.250	0.354	2.000	0.667
9998*	Queue	3.000	0.000	1.417	0.410
9999*	Digging	3.000	0.167	2.750	1.688
Negative					
2800	Sad child	1.333	0.222	4.167	0.639
3010	Mutilation	1.000	0.000	4.333	0.222
3015	Accident	1.000	0.000	4.833	0.139

3064	Mutilation	1.000	0.000	4.250	0.188
3080	Mutilation	1.000	0.000	4.500	0.583
3100	Burn victim	1.000	0.000	4.250	0.188
3102	Burn victim	1.000	0.000	4.667	0.222
3130	Mutilation	1.000	0.000	4.500	0.583
3168	Mutilation	1.000	0.000	4.833	0.139
3170	Baby tumour	1.000	0.000	4.667	0.222
3180	Battered female	1.333	0.222	3.833	0.306
3261	Tumour	1.083	0.076	4.417	0.243
3266	Injury	1.000	0.000	4.583	0.243
3400	Severed hand	1.167	0.306	4.000	2.000
3530	Attack	1.167	0.139	4.083	0.243
6213	Terrorist	1.667	0.222	3.167	1.472
6243	Aimed gun	1.500	0.250	3.250	0.688
6312	Abduction	1.417	0.243	3.833	0.472
6313	Attack	1.083	0.076	4.250	0.188
6350	Attack	1.417	0.243	4.167	0.639
6370	Attack	1.417	0.243	3.250	0.688
6560	Attack	1.333	0.222	3.667	0.722
6570	Suicide	1.333	0.222	3.667	0.722
6821	Gang	1.667	0.222	3.417	1.410
9040	Starving child	1.083	0.076	4.750	0.188
9050	Plane crash	1.083	0.076	3.833	0.806
9140	Cow	1.500	0.417	3.667	0.222
9181	Dead cows	1.083	0.076	3.333	0.889
9253	Mutilation	1.000	0.000	4.833	0.306
9300	Dirty	1.000	0.000	4.083	0.410
9320	Vomit	1.250	0.188	2.917	1.243
9400	Soldier	1.000	0.000	3.750	0.521
9405	Sliced hand	1.083	0.076	3.500	1.083
9410	Soldier	1.000	0.000	4.917	0.076
9420	Soldier	1.000	0.000	4.417	0.410
9433	Dead man	1.250	0.188	3.833	0.639
9570	Dog	1.000	0.000	3.917	0.910
9571	Cat	1.250	0.188	3.333	1.389
9600	Ship	1.083	0.076	4.167	0.639
9810	KKK rally	1.083	0.076	4.333	0.722
9910	Car accident	1.500	0.250	3.167	0.639

Positive

1440	Seal	4.083	0.243	3.000	0.667
1460	Kitten	4.583	0.243	3.250	0.854

1610	Rabbit	4.083	0.243	2.333	0.556
1710	Puppies	4.500	0.250	2.917	0.910
1750	Bunnies	4.583	0.243	2.500	0.583
1920	Porpoise	4.333	0.222	2.917	1.076
2040	Baby	4.167	0.139	2.500	0.583
2091	Girls	4.417	0.243	2.583	0.743
2160	Father	4.000	0.167	2.167	0.806
2165	Father	4.167	0.306	2.500	0.750
2216	Children	4.167	0.139	2.500	0.583
2311	Mother	4.583	0.243	3.333	0.722
2340	Family	4.250	0.188	2.750	0.188
2360	Family	4.250	0.188	2.250	1.021
2530	Couple	4.167	0.139	1.917	0.910
4603	Romance	4.083	0.076	2.250	1.188
5480	Fireworks	4.250	0.188	3.500	1.250
5594	Sky	4.333	0.222	3.083	1.243
5600	Mountains	4.417	0.410	3.500	0.750
5621	Sky divers	4.167	0.472	3.083	1.243
5623	Windsurfers	4.417	0.243	3.417	0.910
5629	Hiker	4.333	0.222	4.083	0.910
5760	Nature	4.333	0.222	2.333	0.722
5780	Nature	4.083	0.243	3.083	0.576
5830	Sunset	4.583	0.243	3.333	1.389
5831	Seagulls	4.333	0.389	2.667	0.889
7280	Wines	4.000	0.000	2.250	1.188
7325	Watermelon	4.083	0.243	3.083	0.576
7330	Ice cream	4.250	0.188	2.750	0.854
8120	Athlete	4.000	0.167	2.750	0.688
8185	Sky divers	4.583	0.243	3.500	2.583
8190	Skier	4.417	0.243	3.917	1.076
8200	Water skier	4.000	0.167	2.750	0.688
8380	Athletes	4.167	0.139	3.167	0.806
8420	Tubing	4.000	0.000	2.000	0.500
8496	Water slide	4.333	0.222	2.333	0.389
8500	Gold	4.167	0.139	3.000	1.000
9951	Islands	4.667	0.222	3.583	0.410
9952	City	4.000	0.167	2.667	1.889
9958	Girl	4.167	0.139	2.333	0.722
9959	Penguins	4.333	0.222	2.750	0.521

Experiment 6 Contexts
Valence and arousal scale 1-9

IAPS Code	Description	Valence		Arousal	
		Mean	Variance	Mean	Variance
Neutral, No people					
5250	Nature	6.08	0.243	3.64	0.639
5390	Boat	5.59	0.243	2.88	0.583
5395	Boat	5.34	0.167	4.23	0.306
5510	Mushroom	5.15	0.250	2.82	0.222
5534	Nature	4.84	0.188	3.14	0.410
5535	Stilllife	4.81	0.243	4.11	1.083
5740	Plant	5.21	0.222	2.59	0.243
5900	Desert	5.93	0.222	4.38	0.222
6150	Outlet	5.08	0.243	3.22	0.139
7000	Rolling pin	5	0.472	2.42	0.688
7002	Towel	4.97	0.139	3.16	2.000
7009	Mug	4.93	0.243	3.01	0.188
7010	Basket	4.79	0.222	1.76	1.389
7020	Fan	4.97	0.243	2.17	0.243
7031	Shoes	4.52	0.243	2.03	0.076
7050	Hair dryer	4.93	0.243	2.75	0.688
7090	Book	5.19	0.076	2.61	0.639
7100	Fire hydrant	5.24	0.250	2.89	0.139
7130	Truck	4.77	0.000	3.35	0.889
7140	Bus	5.5	0.389	2.92	0.472
7160	Fabric	5.02	0.076	3.07	0.583
7170	Light bulb	5.14	0.222	3.21	0.806
7182	Checkerboard	5.16	0.139	4.06	0.521
7184	Abstract art	4.84	0.139	3.66	0.722
7185	Abstract art	4.97	0.417	2.64	1.243
7186	Abstract art	4.63	0.243	3.6	0.222
7190	Clock	5.55	0.243	3.84	0.306
7195	Teeth	6.02	0.188	4.54	0.639
7211	Clock	4.81	0.188	4.2	0.222
7217	Clothes rack	4.82	0.306	2.43	0.188
7234	Ironing board	4.23	0.306	2.96	0.188
7237	Abstract art	5.43	0.222	3.88	0.722
7491	Building	4.82	0.222	2.39	1.410
7500	Building	5.33	0.243	3.26	0.243
7510	Skyscraper	6.05	0.167	4.52	0.722
7700	Office	4.25	0.000	2.95	0.410

7705	Cabinet	4.77	0.076	2.65	1.472
7820	Agate	5.39	0.410	4.21	0.639
9955*	Bridge	4.97	0.243	4.12	0.188
9964*	Manifold	5.02	0.188	4.73	0.910

Neutral, With people

2190	Man	4.83	0.076	2.41	0.910
2200	Neutral face	4.79	0.222	3.18	0.222
2210	Neutral face	4.38	0.243	3.56	0.410
2214	Neutral man	5.01	0.167	3.46	0.722
2215	Neutral man	4.63	0.000	3.38	0.583
2320	Girl	6.17	0.167	2.9	0.188
2372	Woman	5.48	0.243	4.09	0.583
2381	Girl	5.25	0.243	3.04	0.188
2383	Secretary	4.72	0.243	3.41	0.188
2410	Boy	4.62	0.139	4.13	0.243
2480	Elderly man	4.77	0.306	2.66	0.639
2487	Musician	5.2	0.243	4.05	2.000
2495	Man	5.22	0.389	3.19	0.306
2514	Woman	5.19	0.243	3.5	0.688
2575	Propellor	5.46	0.139	4.16	0.222
2580	Chess	5.71	0.222	2.79	0.521
2749	Smoking	5.04	0.188	3.76	0.410
2850	Tourist	5.22	0.188	3	0.639
2870	Teenager	5.31	0.000	3.01	0.139
5410	Violinist	6.11	0.188	3.29	0.639
5455	Cockpit	5.79	0.243	4.56	0.188
7550	Office	5.27	0.417	3.95	1.410
7620	Jet	5.78	0.076	4.92	0.889
7640	Skyscraper	5	0.250	6.03	1.083
9070	Boy	5.01	0.222	3.63	0.722
9700	Workers	4.77	0.250	3.21	0.639
9961*	Truck	5.1	0.243	3.6	0.222
9965*	Snow trek	4.7	0.222	3.9	0.306
9981*	Roadworks	4.6	0.222	3.2	0.722
9982*	Working	5.1	0.243	3.9	0.243
9983*	Street	4.3	0.139	2.9	0.139
9985*	Boat	5.3	0.243	4.1	1.472
9986*	Camp	5	0.076	3.8	0.222
9988*	Snow	5.2	0.472	3.7	0.806
9990*	Dock	4.6	0.243	3.6	0.688
9991*	Foggy	4.1	0.306	3.1	1.389

9992*	Bikes	4.7	0.188	2.9	1.243
9993*	Café	5.4	0.243	3.8	0.472
9994*	Ticket office	4.3	0.222	2.4	0.076
9999*	Digging	4.7	0.410	3.9	0.243

Negative, No people

1050	Snake	3.46	0.243	6.87	1.389
1052	Snake	3.5	0.243	6.52	0.243
1111	Snake	3.25	0.243	5.2	0.188
1220	Spider	3.47	0.243	5.57	1.243
1275	Cockroaches	3.3	0.188	4.81	0.639
5971	Tornado	3.49	0.243	6.65	0.521
5972	Tornado	3.45	0.139	6.34	0.306
6020	Electric chair	3.41	0.243	5.58	0.910
7380	Cockroach pizza	2.46	0.222	5.88	0.243
9000	Cemetery	2.55	0.222	4.06	0.139
9080	Wires	4.07	0.222	4.36	0.222
9140	Cow	2.19	0.306	5.38	0.222
9181	Dead cows	2.26	0.243	5.39	0.639
9280	Smoke	2.8	0.306	4.26	0.806
9300	Dirty	2.26	0.139	6	0.410
9320	Vomit	2.65	0.222	4.93	0.583
9340	Garbage	2.41	0.139	5.16	0.722
9470	Ruins	3.05	0.250	5.05	0.222
9560	Duck oil slick	2.12	0.076	5.5	0.688
9561	Sick kitten	2.68	0.222	4.79	0.722
9570	Dog	1.68	0.410	6.14	0.472
9571	Cat	1.96	0.000	5.64	0.243
9600	Ship	2.48	0.167	6.46	0.222
9620	Shipwreck	2.7	0.243	6.11	0.188
9630	Bomb	2.96	0.243	6.06	0.688
9830	Cigarettes	2.54	0.000	4.86	0.639
9911	Car accident	2.3	0.167	5.76	1.083
9957	Wall	2.26	0.472	5.88	0.889
10004*	Blood tiles	2.65	0.243	4.06	0.188
10005*	Blood stain	2.41	0.389	4.36	0.639
10006*	Knife	3.05	0.243	5.38	0.076
10007*	Gutted building	2.12	0.188	5.39	0.583
10008*	Execution chamber	2.68	0.076	4.26	0.722
10010*	Wrecked building	1.68	0.188	6	2.000
10011*	Bomb blast	1.96	0.417	4.93	0.188
10012*	Bomb blast	2.48	0.076	5.16	0.410

10013*	Scorpion	2.7	0.243	6.06	0.306
10014*	Crocodile	2.96	0.222	4.86	0.139
10015*	Fire	3.02	0.250	5.76	1.410
10016*	Explosion	2.84	0.188	5.88	1.472

Negative, With people

2205	Hospital	1.95	0.167	4.53	0.910
2352.2	Bloody kiss	2.09	0.243	6.25	0.243
2691	Riot	3.04	0.139	5.85	0.639
2692	Bomb	3.36	0.000	5.35	0.243
2710	Drug addict	2.52	0.076	5.46	1.389
2722	Jail	3.47	0.000	3.52	0.139
2751	Drink driving	2.67	0.243	5.18	0.306
2800	Sad child	1.78	0.243	5.49	0.188
3010	Mutilation	1.71	0.410	7.16	0.222
3015	Mutilation	1.52	0.076	5.9	0.722
3060	Mutilation	1.79	0.222	7.12	0.188
3062	Mutilation	1.87	0.222	5.78	0.722
3064	Mutilation	1.45	0.472	6.41	0.188
3080	Mutilation	1.48	0.417	7.22	0.688
3102	Burn victim	1.4	0.167	6.58	0.889
3130	Mutilation	1.58	0.250	6.97	0.410
3140	Dead body	1.83	0.389	6.36	0.139
3168	Mutilation	1.56	0.243	6	0.306
3170	Baby tumour	1.46	0.243	7.21	2.000
3180	Battered female	1.92	0.243	5.77	0.521
3181	Battered female	2.3	0.076	5.06	0.076
3230	Dying man	2.02	0.243	5.41	0.583
3261	Tumour	1.82	0.222	5.75	1.083
3266	Injury	1.56	0.139	6.79	0.410
3530	Attack	1.8	0.243	6.82	0.583
6312	Abduction	2.48	0.222	6.37	0.243
6313	Attack	1.98	0.222	6.94	0.639
6560	Attack	2.16	0.222	6.53	0.472
6821	Gang	2.38	0.243	6.29	0.806
9040	Starving child	1.67	0.188	5.82	0.639
9050	Plane crash	2.43	0.306	6.36	0.722
9252	Dead body	1.98	0.188	6.64	1.243
9253	Mutilation	2	0.243	5.53	0.188
9265	Hung man	2.6	0.243	4.34	0.222
9415	Handicapped	2.82	0.188	4.91	1.410
9433	Dead man	1.84	0.250	5.89	1.472

Fountain pen	3.083	0.076	1.333	0.389
Fridge	3.000	0.000	1.417	0.243
Frog	3.083	0.076	1.333	0.222
Funnel	3.083	0.076	1.250	0.188
Garage	3.083	0.076	1.667	0.722
Garden table	3.250	0.188	1.750	0.354
Garlic	3.083	0.076	1.750	0.521
Glass	3.083	0.076	1.667	0.889
Glove	3.000	0.000	1.000	0.000
Goggles	2.833	0.139	1.417	0.243
Go-kart	2.917	0.076	1.333	0.389
Goldfish	2.917	0.076	1.833	0.806
Golf ball	3.000	0.000	1.500	0.917
Golf club	2.917	0.076	1.417	0.576
Grand piano	2.917	0.076	1.417	0.410
Graph	3.167	0.306	1.583	0.410
Green tea	3.000	0.000	1.000	0.000
Guitar	3.167	0.306	1.583	0.743
Hair dryer	2.917	0.076	1.667	0.389
Hairbrush	3.000	0.000	1.500	0.417
Hammer	3.083	0.076	1.167	0.139
HammocK	3.000	0.000	1.333	0.222
Hand	3.083	0.076	1.833	1.139
Handbag	3.000	0.000	1.333	0.222
Hat	3.000	0.000	1.583	0.743
Headphones	3.000	0.167	1.083	0.972
Heater	3.083	0.076	1.417	0.743
Helicopter	3.083	0.076	1.583	0.576
Helmet	3.000	0.333	1.500	0.417
Hi-fi	3.000	0.167	1.500	0.583
Highchair	2.917	0.076	1.333	0.222
Holly	3.083	0.076	1.333	0.389
Hoover	3.083	0.076	1.833	0.972
Hose	3.000	0.000	1.167	0.139
Hubcap	3.083	0.076	1.167	0.139
Iron	3.000	0.000	1.167	0.139
Ironing board	3.000	0.000	1.167	0.139
Jacket	3.083	0.076	2.000	0.500
Jeans	3.000	0.167	1.417	0.576
Jetski	3.000	0.000	1.083	0.076
Jug	3.167	0.139	1.250	1.188
Juicer	3.167	0.139	1.917	0.576
Jumper	2.833	0.306	1.917	0.743
Jumpleads	2.917	0.410	1.417	0.639

9800	Skinhead	2.04	0.306	6.05	0.222
9810	KKK rally	2.09	0.188	6.62	0.639
9910	Car accident	2.06	0.243	6.02	0.222
9920	Car accident	2.5	0.139	5.76	0.688
9966*	Funeral	2.98	0.306	5.42	0.188

Critical objects for experiments 1 - 6
Valence and arousal scale 1-5

Description	Valence		Arousal	
	Mean	Variance	Mean	Variance
Adaptor	3.083	0.076	1.833	1.139
Am football helmet	3.083	0.076	1.333	0.222
American football	2.917	0.243	1.750	0.854
Anchor	3.083	0.076	1.167	0.139
Apple	3.000	0.000	1.333	0.222
Armchair	2.833	0.306	1.333	0.972
Avocado	3.000	0.000	1.167	0.139
Bag	3.083	0.243	1.167	0.354
Bagel	3.000	0.333	1.500	0.417
Bagpipes	3.000	0.167	1.500	0.583
Balloon	3.083	0.243	1.667	0.722
Bananna	3.083	0.076	1.667	0.722
Barbeque	3.250	0.188	1.750	0.354
Barrel	3.167	0.306	1.583	0.410
Baseball	2.917	0.243	1.167	1.722
Basket	2.917	0.410	1.417	0.639
Bass drum	2.833	0.139	1.417	0.243
Bathtub	2.833	0.306	1.917	0.743
Battery	3.083	0.243	1.500	1.167
Bed	3.083	0.076	1.500	1.333
Bedding	3.000	0.000	1.500	0.917
Bell	2.917	0.076	1.833	0.806
Belt	3.000	0.000	1.167	0.139
Bench	3.083	0.076	1.333	0.389
Bicycle	3.000	0.000	1.000	0.000
Bikelock	3.000	0.000	1.250	0.688
Bikewheel	3.083	0.076	1.417	0.743
Bin	3.000	0.000	1.167	0.139
Binoculars	3.000	0.000	1.083	0.076
Biscuit	3.000	0.000	1.000	0.000
Boat	2.917	0.076	1.417	0.576

Book	3.000	0.000	1.417	0.243
Bookshelves	3.000	0.000	1.250	0.688
Boot	3.000	0.000	1.583	0.743
Bottleopener	3.083	0.076	1.250	0.188
Bowl	3.083	0.076	1.750	0.521
Bowtie	3.167	0.139	1.417	0.410
Box	3.000	0.000	1.083	0.076
Bread	3.167	0.139	1.250	1.188
Bridge	2.917	0.076	1.667	0.389
Broom	3.000	0.167	1.083	0.972
Brush	3.000	0.000	1.333	0.222
Bugle	3.083	0.076	1.667	0.889
Bulldozer	3.083	0.076	1.667	0.722
Bus	2.917	0.076	1.417	0.410
Button	3.000	0.000	1.333	0.389
Cabinet	3.000	0.000	1.167	0.139
Cable	2.917	0.076	1.333	0.389
Cactus	3.167	0.139	1.917	0.576
Cafetiere	3.000	0.000	1.500	0.417
Calculator	3.083	0.076	1.583	0.576
Camel	3.083	0.410	1.583	1.688
Camera	2.917	0.076	1.333	0.222
Campervan	3.083	0.076	1.833	0.972
Camping kit	3.083	0.076	2.000	0.500
Candle	3.083	0.076	1.167	0.139
Candle 2	3.167	0.306	1.583	0.743
Cap	3.250	0.354	1.583	0.667
Caravan	3.000	0.167	1.417	0.576
Cards	3.000	0.000	1.500	0.583
Carrots	3.000	0.000	1.167	0.139
CD	2.917	0.076	1.833	0.806
CD player	3.000	0.000	1.583	0.743
Chair	3.000	0.000	1.000	0.000
Chess	3.167	0.139	1.917	0.576
Chestofdrawers	3.167	0.139	1.417	0.410
Chimney	2.833	0.306	1.333	0.972
Chubb	3.083	0.076	1.833	0.972
Cigar	3.000	0.167	1.500	0.583
Circuitboard	3.083	0.243	1.167	0.354
Clip	3.000	0.333	1.500	0.417
Clock	3.083	0.076	2.000	0.500
Coach	3.083	0.076	1.667	0.722
Coconut	3.000	0.000	1.333	0.222
Comb	2.917	0.076	1.667	0.389

Compass	3.000	0.167	1.417	0.576
Connector	2.917	0.243	1.167	1.722
Cooler	3.083	0.076	1.167	0.139
Corkscrew	2.917	0.076	1.333	0.222
Corkscrew 2	3.000	0.000	1.333	0.389
Cot	3.083	0.076	1.417	0.743
Cow	3.083	0.243	1.667	0.722
Crane	3.250	0.354	1.583	0.667
Crayon	3.167	0.306	1.583	0.410
Cube	2.917	0.076	1.417	0.576
Cup	3.083	0.076	1.500	1.333
Curtain	2.917	0.076	1.333	0.389
Cushion	3.083	0.076	1.333	0.222
Cycling helmet	3.000	0.000	1.250	0.688
Dart	3.000	0.000	1.083	0.076
Dart 2	3.000	0.000	1.083	0.076
Decorated spoon	3.000	0.000	1.167	0.139
Denim	3.083	0.243	1.500	1.167
Desk	3.083	0.076	1.750	0.521
Dice	2.833	0.306	1.917	0.743
Die	3.000	0.000	1.333	0.222
Dinghy	3.000	0.000	1.500	0.417
Door	3.083	0.076	1.167	0.139
Doorhandle	3.000	0.000	1.500	0.583
Dress	3.000	0.000	1.417	0.243
Drill	3.250	0.188	1.750	0.354
Drum	3.083	0.076	1.833	1.139
Dummy	2.917	0.243	1.750	0.854
Dustpan	3.000	0.167	1.083	0.972
Eagle	2.917	0.410	1.417	0.639
Egg	3.000	0.000	1.000	0.000
Envelope	3.083	0.076	1.667	0.722
Escalator	2.833	0.139	1.417	0.243
Extinguisher	3.083	0.076	1.583	0.576
Fan	3.000	0.000	1.167	0.139
Fax	3.167	0.306	1.583	0.743
Feet	3.167	0.139	1.250	1.188
Fence	3.083	0.076	1.667	0.889
Filofax	3.000	0.000	1.250	0.688
Fire engine	3.000	0.000	1.167	0.139
Fireplace	3.083	0.076	1.250	0.188
Floppy disk	2.917	0.076	1.417	0.410
Folder	3.083	0.410	1.583	1.688
Football	3.000	0.000	1.500	0.917

Kettle	3.000	0.000	1.250	0.688
Key	3.167	0.139	1.417	0.410
Keyboard	3.083	0.243	1.667	0.722
Kite	2.917	0.243	1.750	0.854
Ladder	3.250	0.354	1.583	0.667
Ladle	3.000	0.000	1.250	0.688
Lamp	3.000	0.000	1.333	0.389
Lantern	3.000	0.000	1.167	0.139
Laptop	3.083	0.410	1.583	1.688
Laptop 2	2.833	0.306	1.333	0.972
Lawnmower	3.083	0.243	1.167	0.354
Leaf	3.083	0.243	1.500	1.167
Leather gloves	3.083	0.076	1.500	1.333
Leather jacket	3.083	0.076	1.667	0.722
Lights	3.000	0.000	1.083	0.076
Lipstick	2.917	0.243	1.167	1.722
Lizard	3.000	0.000	1.500	0.583
Lobster	3.000	0.000	1.500	0.417
Lorry	2.917	0.076	1.833	0.806
Mailbox	3.000	0.000	1.083	0.076
Makeup	3.250	0.354	1.583	0.667
Manhole	3.000	0.000	1.333	0.222
Marbles	3.000	0.000	1.083	0.076
Mattress	3.000	0.000	1.250	0.688
Measuring Jug	3.083	0.076	1.333	0.222
Medal	3.083	0.076	1.167	0.139
Medieval Helmet	3.000	0.000	1.333	0.389
Metronome	3.083	0.076	1.500	1.333
Microscope	3.083	0.243	1.667	0.722
Microwave	2.917	0.410	1.417	0.639
Mirror	3.000	0.000	1.167	0.139
Mixer	3.000	0.000	1.167	0.139
Mobile phone	3.083	0.076	1.417	0.743
Monitor	3.000	0.000	1.500	0.917
Moon	2.917	0.076	1.417	0.576
Moped	3.167	0.306	1.583	0.743
Motorway	3.000	0.000	1.250	0.688
Mouse	3.167	0.306	1.583	0.410
Mousetrap	3.000	0.000	1.000	0.000
Mug	3.000	0.167	1.500	0.583
Multisocket	3.083	0.076	1.667	0.722
Mushroom	3.000	0.000	1.417	0.243
Nautical Compass	3.083	0.076	1.750	0.521
Neck whistle	3.083	0.076	1.667	0.722

Necklace	3.000	0.000	1.167	0.139
Notebook	3.000	0.000	1.167	0.139
Nutcracker	3.083	0.243	1.500	1.167
Office Chair	2.833	0.139	1.417	0.243
Oil rig	3.083	0.076	1.167	0.139
Oilcan	3.083	0.410	1.583	1.688
Orange	3.083	0.076	1.667	0.889
Oven	3.000	0.333	1.500	0.417
Ovenglove	3.083	0.076	1.250	0.188
Paddle	3.083	0.076	1.583	0.576
Padlock	2.917	0.076	1.333	0.222
Paperclip	3.167	0.139	1.917	0.576
Pear	3.000	0.000	1.583	0.743
Peg	3.167	0.139	1.250	1.188
Pen	3.000	0.000	1.500	0.583
Peppermill	2.917	0.243	1.750	0.854
Peppers	2.917	0.076	1.667	0.389
Pestle & Mortar	3.083	0.076	2.000	0.500
Phone	2.833	0.306	1.917	0.743
Phonebox	3.000	0.000	1.333	0.222
Photocopier	3.000	0.167	1.417	0.576
Piano	2.917	0.076	1.417	0.410
Pills	3.083	0.076	1.333	0.389
Pineapple	3.083	0.076	1.833	1.139
Pipe	2.833	0.306	1.333	0.972
Pipe2	3.000	0.167	1.083	0.972
Pizza cutter	3.250	0.188	1.750	0.354
Pliers	3.083	0.243	1.167	0.354
Plug	3.000	0.000	1.000	0.000
Pool	2.917	0.243	1.167	1.722
Pot	3.083	0.076	1.833	0.972
Prawn	3.167	0.139	1.417	0.410
Printer	2.917	0.076	1.333	0.389
Propellor	3.083	0.076	1.500	1.333
Pumpkin	3.083	0.076	1.667	0.889
Pyramid	3.000	0.000	1.000	0.000
Radio	3.083	0.243	1.167	0.354
Razor	3.083	0.076	1.333	0.389
Recorder	3.000	0.000	1.500	0.917
Red lipstick	2.917	0.076	1.417	0.576
Remote	3.000	0.000	1.250	0.688
Ring	3.167	0.139	1.417	0.410
Rucksack	2.917	0.076	1.667	0.389
Rug	3.000	0.000	1.167	0.139

Saddle	3.167	0.139	1.917	0.576
Safe	3.000	0.000	1.167	0.139
Sandcastle	2.917	0.410	1.417	0.639
Sandles	3.083	0.076	1.833	0.972
Sandwich	3.083	0.076	1.667	0.722
Satellite	3.083	0.076	1.250	0.188
Saw	3.083	0.076	1.333	0.222
Scales	3.000	0.000	1.167	0.139
Scanner	3.000	0.000	1.000	0.000
Scarf	2.917	0.243	1.167	1.722
Scissors	3.000	0.000	1.333	0.222
Scoop	2.917	0.076	1.333	0.222
Screwdriver	3.167	0.306	1.583	0.743
Sea Helicopter	3.000	0.000	1.333	0.222
Sharpener	3.000	0.000	1.500	0.583
Shaver	3.250	0.354	1.583	0.667
Shell	3.000	0.000	1.333	0.389
Shelves	3.000	0.000	1.500	0.417
Shield	3.000	0.167	1.083	0.972
Shirt	3.000	0.000	1.083	0.076
Shoe	3.167	0.306	1.583	0.410
Shorts	3.083	0.076	1.167	0.139
Shower	3.000	0.000	1.417	0.243
Shredder	3.000	0.000	1.083	0.076
Sieve	2.917	0.076	1.833	0.806
Sink	3.000	0.167	1.417	0.576
Skate	3.083	0.076	1.667	0.722
Skateboard	2.917	0.076	1.333	0.389
Skirt	2.917	0.243	1.750	0.854
Sleepingbag	3.083	0.076	1.833	1.139
Slide	2.833	0.139	1.417	0.243
Slippers	3.083	0.076	1.417	0.743
Socks	3.083	0.076	1.167	0.139
Sofa	3.083	0.243	1.500	1.167
Spanner	3.083	0.410	1.583	1.688
Spatula	2.833	0.306	1.917	0.743
Speaker	3.000	0.000	1.583	0.743
Sphigomanometer	3.000	0.000	1.167	0.139
Spinning wheel	3.000	0.333	1.500	0.417
Sponge	3.083	0.076	1.583	0.576
Spoon	3.083	0.076	1.750	0.521
Spring	2.833	0.306	1.333	0.972
Stadium	2.917	0.076	1.417	0.410
Stamp	3.000	0.167	1.500	0.583

Stapler	3.000	0.000	1.250	0.688
Starfish	3.083	0.243	1.667	0.722
Stilleto shoe	3.167	0.139	1.250	1.188
Stool	3.250	0.188	1.750	0.354
Suitcase	3.083	0.076	2.000	0.500
Sunglasses	3.083	0.076	1.167	0.139
Sweeper	3.083	0.076	1.667	0.889
Sweetcorn	2.917	0.076	1.417	0.410
Swing	3.000	0.000	1.583	0.743
Switch	3.083	0.076	1.583	0.576
Table	3.083	0.076	1.750	0.521
Tabletennis	3.000	0.000	1.333	0.222
Tap	3.083	0.076	1.250	0.188
Tape-measure	2.917	0.243	1.167	1.722
Teabag	2.917	0.076	1.833	0.806
Teapot	3.000	0.000	1.167	0.139
Teepee	2.917	0.076	1.333	0.222
Telescope	3.000	0.000	1.417	0.243
Television	3.000	0.000	1.000	0.000
Tent	2.917	0.076	1.333	0.389
Thermometer	2.833	0.139	1.417	0.243
Thermos flask	3.250	0.354	1.583	0.667
Thread	3.083	0.076	1.333	0.389
Tie	3.000	0.167	1.083	0.972
Tinopener	3.083	0.076	1.833	1.139
Tissues	3.000	0.167	1.500	0.583
Toaster	3.167	0.139	1.250	1.188
Toiletbrush	3.000	0.000	1.167	0.139
Toiletroll	3.083	0.076	1.500	1.333
Tomato	2.833	0.306	1.917	0.743
Toothbrush	2.917	0.076	1.417	0.576
Torch	3.000	0.000	1.250	0.688
Totempole	2.917	0.410	1.417	0.639
Tower	3.167	0.139	1.917	0.576
Tractor	3.167	0.306	1.583	0.743
Traffic cone	2.917	0.243	1.750	0.854
Traffic lights	3.000	0.000	1.000	0.000
Trainer	3.000	0.000	1.167	0.139
Tree	3.083	0.076	2.000	0.500
Tricycle	3.083	0.076	1.667	0.722
Trowel	3.000	0.000	1.250	0.688
Trumpet	3.083	0.076	1.833	0.972
T-shirt	3.000	0.000	1.500	0.917
TV set	3.167	0.306	1.583	0.410

Typewriter	3.000	0.000	1.167	0.139
Umbrella	3.000	0.000	1.500	0.417
Van	3.167	0.139	1.417	0.410
Vase	3.250	0.188	1.750	0.354
Video	3.000	0.167	1.417	0.576
Violin	3.083	0.243	1.667	0.722
Wallet	3.083	0.076	1.333	0.222
Wardrobe	3.000	0.000	1.333	0.222
Washbasin	3.083	0.243	1.167	0.354
Watch	3.083	0.076	1.667	0.722
Watering can	3.000	0.000	1.083	0.076
Wetsuit	3.083	0.410	1.583	1.688
Wheel	3.083	0.076	1.167	0.139
Whistle	3.083	0.243	1.500	1.167
Window	3.000	0.000	1.500	0.583
Wok	2.833	0.306	1.333	0.972
Wooden ladder	3.000	0.000	1.083	0.076
Yacht	2.917	0.076	1.667	0.389

References

Adolphs R, Baron-Cohen S, Tranel D (2002) Impaired recognition of social emotions following amygdala damage. J Cogn Neurosci. 14(8): 1264-1274

Adolphs R, Cahill L, Schul R & Babinsky, R. (1997) Impaired declarative memory for emotional material following bilateral amygdala damage in humans. Learn Mem 4 (3): 291-300.

Adolphs R, Denburg NL, Tranel D (2001) The amygdala's role in long-term declarative memory for gist and detail. Behav Neurosci. 115(5): 983-992

Adolphs R, Tranel D, Damasio H, Damasio A (1994) Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372(6507): 669-672

Adolphs,R., Tranel,D. & Denburg,N.(2000) Impaired emotional declarative memory following unilateral amygdala damage. Learn. Mem. 7: 180-186.

Adolphs R, Tranel D (2004) Impaired judgments of sadness but not happiness following bilateral amygdala damage. J Cogn Neurosci. 16(3): 453-462

Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 22: 425-489.

Aggleton JP, Pearce JM (2001) Neural systems underlying episodic memory: insights from animal research. Phil. Trans. R. Soc. Lond. B 356: 1467-1482

Allan K, Wilding EL, Rugg MD (1998) Electrophysiological evidence for dissociable processes contributing to recollection. Acta Psychologia 98(2-3): 231-252

Amaral DG, Price JP, Pitkanen A, Carmichael ST (1992) Anatomical organization of the primate amygdaloid complex. In: The amygdala: Neurobiological aspects of emotion, memory and mental dysfunction (JP Aggleton (Ed.)) pp 255-306. New York: Wiley-Liss

Anagnostaras SG, Gale GD, Fanselow MS (2001) Hippocampus and contextual fear conditioning: recent controversies and advances. Hippocampus 11(1): 8-17

Anderson AK, Christoff K, Panitz D, De Rosa E, Gabrieli JD (2003) Neural correlates of the automatic processing of threat facial signals. J Neurosci. 23(13): 5627-5633

Anderson AK, Phelps EA (2001) Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature 411(6835): 305-309

Anderson AK, Phelps EA (2002) Is the human amygdala critical for the subjective experience of emotion? Evidence of intact dispositional affect in patients with amygdala lesions. J Cogn Neurosci. 14(5): 709-720

Anderson ND, Craik FIM, Naveh-Benjamin M (1998) The attentional demands of encoding and retrieval in younger and older adults 1. Evidence from divided attention costs. Psych Aging 13(3): 405-423

Angrilli A, Palomba D, Cantagallo A, Maietti A, Stegagno L (1999) Emotional impairment after right orbitofrontal lesion in a patient without cognitive deficits. Neuroreport 10(8): 1741-1746

Armony JL, LeDoux JE (2000) How danger is encoded: toward a systems, cellular and computational understanding of cognitive-emotional interactions in fear. In: The New Cognitive Neurosciences (MS Gazzaniga (Ed.)) pp 1067-1080. Cambridge, MA: MIT Press

Arthurs OJ, Boniface S (2002) How well do we understand the neural origins of the fMRI BOLD signal? Trends Neurosci. 25(1): 27-31

Ashburner J, Neelin P, Collins DL, Evans A, Friston KJ (1997) Incorporating prior knowledge into image registration. NeuroImage 6: 344-352

Ashby FG, Isen AM, Turken AU (1999) A Neuropsychological Theory of Positive Affect and its Influence on Cognition. Psychol. Rev. 106(3): 529-550

Asthana B, Nagrani S (1984) Recall and recognition as a function of levels of processing. Psycho-Lingua 14(2): 85-94

Atkinson, R. C. & Juola, J. F. 1974 Search and decision processes in recognition memory. In: Contemporary developmentsin mathematical psychology.Vol. 1. Learning, memory & thinking (DH Krantz, RC Atkinson, RD Luce, P Suppes (Eds.)). San Francisco: Freeman.

Baddeley, AD (1997) Human memory: theory and practice, revised edn. Hove, UK: Psychology Press.

Baddeley AD (2001) The concept of episodic memory. Philos Trans R Soc Lond B Biol Sci. 356(1413): 1345-1350

Baddeley AD, Hitch GJ (1974) Working memory. In: Recent advances in learning and motivation, vol. 8 (G. A. Bowers (Ed.)) pp. 47-89. NewYork: Academic Press.

Baker SC, Frith CD, Dolan RJ (1997) The interaction between mood and cognitive function studied with PET. Psychol Med. 27(3): 565-578

Bauer RM (1998) Physiologic measures of emotion. J Clin Neurophysiol. 15(5): 388-396

Bechara A (2004) The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. Brain Cogn. 55(1): 30-40

Bechara A, Damasio H, Damasio AR (2000) Emotion, Decision Making and the Orbitofrontal Cortex. Cereb. Cortex 10(3): 295-307

Bechara A, Damasio H, Damasio AR (2003) Role of the amygdala in decision-making.
Ann N Y Acad Sci. 985: 356-369

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR (1995) Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 269(5227): 1115-1118

Bench CJ, Frackowiak RS, Dolan RJ (1995) Changes in regional cerebral blood flow on recovery from depression. Psychol Med. 25(2): 247-261

Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ (1992) The anatomy of melancholia - focal abnormalities of cerebral blood flow in major depression.
Psychol Med. 22(3): 607-615

Bench CJ, Friston KJ, Brown RG, Frackowiak RS, Dolan RJ (1993) Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychol Med. 23(3): 579-590

Berger H (1929) Uber das elektrekephalogramm des menschen. Archive fur Psychiatrie und Nervenkrankheiten 87: 527-570

Blair RJ (2001) Neurocognitive models of aggression, the antisocial personality disorders and psychopathy. J Neurol Neuosurg Psychiatry 72(6): 727-731

Binnie CD (1987) Recording techniques: montages, electrodes, amplifiers and filters. In: A textbook of clinical neurophysiology (AM Halliday, SR Butler, R Paul (Eds.)) pp 3-22. New York: Wiley

Blaney PH (1986) Affect and memory: A review. Psychol Bull. 99(2): 229-246

Blaxton TA, Theodore WH (1997) The role of the temporal lobes in recognizing visuospatial materials: remembering versus knowing. Brain Cogn 35(1): 5-25

Bliss TV, Collingridge GL (1993). A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361(6407): 31-39

Bliss TV, Gardner-Medwin AR (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetised rabbit following stimulation of the perforant path. J Physiol (Lond) 232(2): 357-374

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetised rabbit following stimulation of the perforant path. J Physiol (Lond) 232(2): 331-356

Bloch F, Hansen WW, Packard M (1946) The nuclear induction experiment. Phys Rev 70: 474-485

Bower GH (1981) Mood and memory. Am Psychol 36(2): 129-148

Bower GH (1992) How might emotions affect learning? In: The handbook of emotion and memory: research and theory. (Christianson SA (Ed)) pp 3-31. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Bozarth MA, Wise RA (1983) Neural substrates of opiate reinforcement. Prog Neuropsychopharmacol Biol Psychiatry 7(4-6): 569-575

Bradley MM, Greenwald MK, Petry MC, Lang PJ (1992) Remembering pictures: pleasure and arousal in memory. J Exp Psychol Learn Mem Cogn. 18(2): 379-390

Bradley MM, Lang PJ (1994) Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. J Behav Ther Exp Psychiatry 25(1): 49-59

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR (1996) Response and habituation of the human amygdala during visual processing of facial expression. Neuron 17(5): 875-887

Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion. Neuron. 19(3): 591-611

Brewer JB, Zhao Z, Desmond JE, Glover GH, Gabrieli JDE (1998) Making memories: brain activity that predicts whether visual experiences will be remembered or forgotten. Science 281: 1185-1187

Brown J (1958) Some tests of the decay theory of immediate memory. Q. J. Exp. Psychol. 10: 12-21

Brown MA, Semelka RC (1999) MRI: Basic Principles and Applications (2nd Edn) New York: Wiley-Liss

Brown MW, Aggleton JP (2001) Recognition memory: What are the roles of the perirhinal cortex and hippocampus? Nat. Rev. Neurosci. 2: 51–61

Buchanan TW, Lovallo WR (2001) Enhanced memory for emotional material following stress-level cortisol treatment in humans. Psychoneuroendocrinology 26(3): 307-317

Büchel C, Dolan RJ, Armony JL, Friston KJ (1999) Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related fMRI. J. Neurosci. 19(24): 10869-10876

Büchel C, Friston KJ (1997) Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. Cereb Cortex 7(8): 768-778

Büchel C, Morris J, Dolan RJ, Friston KJ (1998) Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron 20(5): 947-957

Buckner RL, Koutstaal W, Schacter DL, Dale AM, Rotte MR, Rosen BR (1998) Functional-anatomic study of episodic retrieval: II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. NeuroImage 7: 163– 175.

Buckner RL, Petersen SE, Ojemann JG, Miezin FM, Squire LR, Raichle ME (1995) Functional anatomical studies of explicit and implicit memory retrieval tasks. J Neurosci. 15(1): 12-29

Bullmore E, Brammer M, Williams SC, Rabe-Hesketh S, Janot N, David A, Mellers J, Howard R, Sham P (1996) Statistical methods of estimation and inference for functional MR image analysis. Magn Reson Med 35(2): 261-277

Burke A, Heuer F, Reisberg D (1992) Remembering emotional events. Mem Cogn 20(3): 277-290

Burstein A (1985) Posttraumatic flashbacks, dream disturbances, and mental imagery. J Clin Psychiatry 46(9): 374-378

Butterworth B, Cipolotti L, Warrington EK (1996) Short-term memory impairment and arithmetical ability. Q.J. Exp. Psychol 49(1) 251-262

Cabeza R, Nyberg L (2000) Neural Bases of Learning and Memory: Functional Neuroimaging Evidence. Curr. Opin. Neuro. 13(4): 415-421

Cabeza R, Rao SM, Wagner AD, Mayer AR, Schacter DL (2001) Can medial temporal lobe regions distinguish true from false? An event-related functional MRI study of veridical and illusory recognition memory. Proc Natl Acad Sci U S A. 98(8): 4805-4810

Cacioppo JT, Crites SL, Gardner WL (1996) Attitudes to the right: Evaluative processing is associated with lateralized late positive event-related brain potentials. Personality and Social Psychology Bulletin 22: 1205-1219

Cahill L. (1999) A Neurobiological Perspective on Emotionally Influenced, Long-term Memory. Semin. Clin. Neuropsychiatry 4(4): 266-273

Cahill L, Alkire MT (2003) Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. Neurobiol Learn Mem. 79(2): 194-198

Cahill L, Gorski L, Le K (2003) Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. Learn Mem. 10(4): 270-274

Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL (1996) Amygdala activity at encoding correlated with long-term free recall of emotional information. Proc Natl Acad Sci USA 93: 8016-8021

Cahill L, McGaugh JL (1998) Mechanisms of emotional arousal and lasting declarative memory. Trends Neurosci 21: 294-299

Cahill L, Prins B, Weber M, McGaugh JL (1994) Beta-adrenergic activation and memory for emotional events. Nature 371(6499): 702-704

Cahill L, Weinberger NM, Roozendaal B, McGaugh JL (1999) Is the amygdala a locus of "conditioned fear"? Some questions and caveats. Neuron 23(2): 227-228

Calder AJ, Keane J, Manes F, Antoun N, Young AW (2000) Impaired Recognition and Experience of Disgust Following Brain Injury. Nat. Neurosci. 3(11): 1077-1078

Campeau S, Davis M (1995) Prepulse inhibition of the acoustic startle reflex using visual and auditory prepulses: disruption by apomorphine. Psychopharmacology (Berl). 117(3): 267-274

Campos A, Marcos JL, Gonzalez MA (1999) Emotionality of words as related to vividness of imagery and concreteness. Percept Mot Skills 88(3 Pt 2): 1135-1140

Canli T, Desmond JE, Zhao Z, Glover G, Gabrieli JD (1998) Hemispheric asymmetry for emotional stimuli detected with fMRI. Neuroreport 9(14): 3233-3239

Canli T, Zhao Z, Brewer J, Gabrieli JD, Cahill L (2000) Event-related activation in the human amygdala associates with later memory for individual emotional experience.
J Neurosci. 20(19): RC99

Cansino S, Maquet P, Dolan RJ, Rugg MD (2002) Brain activity underlying encoding and retrieval of source memory. Cereb Cortex 12(10): 1048-1056

Canteras NS, Swanson LW (1992) Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. J Comp Neurol. 324(2): 180-194

Carmichael ST, Price JL (1995) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. J Comp Neurol. 363(4): 615-641

Castelluci VF, Carew TJ, Kandel ER (1978) Cellular analysis of the long-term habituation of the gill-withdrawl reflex in *Aplysia californica*. Science 202: 1306-1308

Cavedini P, Riboldi G, Keller R, D'Annucci A, Bellodi L (2002) Frontal lobe dysfunction in pathological gambling patients. Biol Psychiatry 51(4): 334-341

Christianson SA (1992) The Handbook of Emotion and Memory. Hillsdale, NJ: Erlbaum

Clugnet MC, LeDoux JE (1990) Synaptic plasticity in fear conditioning circuits: Induction of LTP in the lateral nucleus of the amygdala by stimulation of the medial geniculate body. J Neurosci. 10(8): 2818-2824

Cippolotti L, Shallice T, Chan D, Fox N, Scahill R, Harrison G, Stevens J, Rudge P (2001) Long-term retrograde amnesia: the crucial role of the hippocampus. Neuropsychologia 39: 151-172

Cohen MR, Niska RW (1980) Localized right cerebral hemisphere dysfunction and recurrent mania. Am J Psychiatry 137(7): 847-848

Cohen NJ, Squire LR (1980) Preserved learning and retention of pattern analyzing skill in amnesia: Dissociation of knowing how and knowing that. Science 210: 207-209

Coles MGH, Gratton G, Kramer AF, Miller GA (1986) Principles of signal acquisition and analysis. In: Psychophysiology: Systems, processes and applications (MGH Coles, E Donchin, SW Porges (Eds.)) London: Guilford Press

Conrad CD, Lupien SJ, Thanasoulis LC, McEwen BS (1997) The effects of type I and type II corticosteroid receptor agonists on exploratory behavior and spatial memory in the Y-maze. Brain Res. 759(1): 76-83

Cooper R, Osselton JW, Shaw JC (1980) EEG Technology (3rd Ed). London: Butterworth and Co Ltd

Courtney SM, Petit L, Haxby JV, Ungerleider LG (1998). The role of prefrontal cortex in working memory: Examining the contents of consciousness. Phil Trans R Soc Lon 353(1377): 1819-1828

Craig AD (2003) Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol. 13(4): 500-505

Craik FIM (1983) On the transfer of information from temporary to permanent memory. Phil Trans R Soc Lon B 302: 341-359

Craik FIM, Govoni R, Naveh-Benjamin M, Anderson ND (1996) The effects of divided attention on encoding and retrieval processes in human memory. J Exp Psych Gen 125(2): 159-180

Creutzfeld OD (2002) Neurophysiological correlates of different functional states of the brain. In: Brain work: The coupling of function, metabolism and blood flow in the brain (DH Ingvar, NA Lassen (Eds.)) Munksgaard.

Critchley H.D., Corfield D.R., Chandler M.P., Mathias C.J. & Dolan R.J. (2000b) Cerebral Correlates of Autonomic Cardiovascular Arousal: a Functional Neuroimaging Investigation in Humans. J. Physiol 523(1): 259-270

Critchley H.D., Elliot R., Mathias C.J. & Dolan R.J. (2000a) Neural Activity Relating to Generation and Representation of Galvanic Skin Conductance Responses: a fMRI study. J. Neurosci. 20(8): 3033-3040

Critchley HD, Mathias CJ, Dolan RJ (2001) Neuroanatomical basis for first- and second-order representations of bodily states. Nat Neurosci. 4(2): 207-212

Critchley HD, Mathias CJ, Dolan RJ (2002a) Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. Neuron. 33(4): 653-663

Critchley HD, Melmed RN, Featherstone E, Mathias CJ, Dolan RJ (2002b) Volitional Control of Autonomic Arousal: a fMRI study. Neuroimage 16(4): 909-919

Curran T (2000) Brain potentials of recollection and familiarity. Mem Cogn 28: 923–938

Curran T (2004) Effects of attention and confidence on the hypothesized ERP correlates of recollection and familiarity. Neuropsychologia 42(8): 1088-1106

Curran T, Cleary AM (2003). Using ERPs to dissociate recollection from familiarity in picture recognition. Cogn Brain Res 15: 191–205

Curran T, Schacter DL, Johnson MK, Spinks R (2001) Brain potentials reflect behavioral differences in true and false recognition. J. Cogn Neurosci. 13: 201-216

Curran T, Tanaka JW, Weiskopf DM (2002). An electrophysiological comparison of visual categorization and recognition memory. Cogn Aff Behav Neurosci 2: 1–18.

Cuthbert BN, Bradley MM, Lang PJ (1996) Probing picture perception: activation and emotion. Psychophysiology 33(2): 103-111

Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ (2000)Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. Biol. Psychol 52: 95-111.

Damasio AR (1995) Descartes' error: emotion, reason and the human brain. New York: GP Putnams Sons.

Damasio AR (1999) The feeling of what happens: body and emotion in the making of consciousness. New York: Harcourt Brace

Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR (1994) The return of Phineas Gage: Clues about the brain from the skull of a famous patient. Science 264(5162): 1102-1105. Erratum in: Science 265(5176): 1159

Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD (2000) Subcortical and Cortical Brain Activity During the Feeling of Self-generated Emotions. Nat. Neurosci. 3(10): 1049-1056

Damasio AR, Tranel D, Damasio H (1990) Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res. 41(2): 81-94

Danion JM, Kauffmann-Muller F, Grange D, Zimmermann MA, Greth P (1995) Affective valence of words, explicit and implicit memory in clinical depression. J. Affect. Disord. 34: 227-234

Davidson RJ, Abercrombie H, Nitschke JB, Putnam K (1999) Regional brain function, emotion and disorders of emotion. Curr Opin Neurobiol. 9(2): 228-234

Davidson RJ, Ekman P, Saron CD, Senulis JA, Friesen WV (1990) Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology. J Pers Soc Psychol. 58(2): 330-341

Davidson RJ, Irwin W (1999) The functional neuroanatomy of emotion and affective style. Trends Cogn Sci. 3(1): 11-21

Davis KD, Kwan CL, Crawley AP, Mikulis DJ (1998) Event-related fMRI of pain: entering a new era in imaging pain. Neuroreport 9(13): 3019-3023

Davis M (1997) Neurobiology of fear responses: the role of the amygdala. J Neuropsychiatry Clin Neurosci. 9(3): 382-402

Debanne D, Thompson SM (1996) Associative long-term depression in the hippocampus in vitro. Hippocampus 6(1): 9-16

Deichmann R, Gottfried JA, Hutton C, Turner R (2003) Optimized EPI for fMRI studies of the orbitofrontal cortex. Neuroimage 19(2): 430-441

Dietrich DE, Kleinschmidt A, Hauser U, Schneider U, Spannhuth CW, Kipp K, Huber TJ, Wieringa BM, Emrich HM, Johannes S (2000) Word recognition memory before and after successful treatment of depression. Pharmacopsychiatry 33(6): 221-228

Dobbins IG, Foley H, Schacter DL, Wagner AD (2002) Executive control during episodic retrieval: Multiple prefrontal processes subserve source memory. Neuron 35(5): 989-996

Dobbins IG, Rice HJ, Wagner AD, Schacter DL (2003) Memory orientation and success: separable neurocognitive components underlying episodic recognition. Neuropsychologia 41(3): 318-333

Dodson CS, Johnson MK (1996) Some problems with the process-dissociation approach to memory. J Exp Psychol Gen 125(2): 181-194

Dolan RJ (2002) Emotion, cognition, and behaviour. Science. 298(5596):1191-1194

Dolan RJ, Lane R, Chua P, Fletcher P (2000) Dissociable temporal lobe activations during emotional episodic memory retrieval. Neuroimage 11: 203-209

Dolcos F, Cabeza R (2002) Event-related potentials of emotional memory: encoding pleasant, unpleasant, and neutral pictures. Cogn Affect Behav Neurosci 2(3): 252-263

Dolcos F, LaBar KS, Cabeza R (2004) Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. Neuron 42(5): 855-863

Donaldson DI, Petersen SE, Buckner RL (2001). Dissociating memory retrieval processes using fMRI: Evidence that priming does not support recognition memory. Neuron 31: 1047– 1059

Donaldson DI, Rugg MD (1998) Recognition memory for new associations: electrophysiological evidence for the role of recollection. Neuropsychologia. 36(5): 377-395

Donaldson W (1996) The role of decision processes in remembering and knowing. Mem.Cogn 18: 23–30

Drevets WC, Raichle ME (1998) Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interaction between emotion and cognition. Cogn. Emotion 12: 353–385

Drevets WC, Videen TQ, MacLeod AK, Haller JW, Raichle ME (1992) PET images of blood flow changes during anxiety: correction. Science 256(5064): 1696

Düzel E, Habib R, Schott B, Schoenfeld A, Lobaugh N, McIntosh AR, Scholz M, Heinze HJ (2003) A multivariate, spatiotemporal analysis of electromagnetic time-frequency data of recognition memory. Neuroimage 18(2): 185-197

Düzel, E., Vargha-Khadem, F., Heinze, H.-J., & Mishkin, M. (2001) Brain activity evidence for recognition without recollection after early hippocampal damage. Proc Natl Acad Sci USA 98: 8101–8106

Düzel, E., Yonelinas, A. P., Mangun, G. R., Heinze, H.-J., & Tulving, E. (1997). Event-related potential correlates of two states of conscious awareness in memory. Proc Natl Acad Sci USA 94: 5973–5978

Eccles JC (1986) Mechanisms of long-term memory. J Physiol 81(4): 312-317

Eichenbaum H (1997) To cortex: thanks for the memories. Neuron 19(3): 481-484

Ekman P (1992) Are there basic emotions? Psych Rev 99(3): 550-553

Eldridge L, Knowlton BJ, Furmanski CS, Bookheimer SY, Engel SA (2000) Remembering episodes: A selective role for the hippocampus during retrieval. Nature Neurosci 11: 1149-1152

El-Ghundi M, Fletcher PJ, Drago J, Sibley DR, O'Dowd BF, George SR (1999) Spatial Learning Deficit in Dopamine D(1) Receptor Knockout Mice. Eur. J. Pharmacol. 383(2): 95-106

Erk S, Kiefer M, Grothe J, Wunderlich AP, Spitzer M, Walter H (2003) Emotional Context Modulates Subsequent Memory Effect. Neuroimage 18(2): 439-447

Fanselow MS, LeDoux JE (1999) Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. Neuron 23(2): 229-232

Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, Fernandez G (2001). Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. Nat Neurosci 4(12): 1259-1264

Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299(5614): 1898-1902

Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RS, Dolan RJ (1995) Brain systems for encoding and retrieval of auditory-verbal memory: An in vivo study in humans. Brain 118 (2): 401-416

Fletcher PC, Frith CD, Rugg MD (1997) The functional neuroanatomy of episodic memory. Trends Neurosci 20: 213-218

Fox E, Russo R, Bowles R, Dotton K (2001) Do threatening stimuli draw or hold attention in visual attention in subclinical anxiety. J Exp Psych Gen 130: 681–700

Fox NA, Davidson RJ (1988) Patterns of electrical activity during facial signs of emotion in 10-month old infants. Develop Psychol 24: 230-236

Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Mazziotta JC (Eds.) (2003) Human Brain Function II. London: Elsevier

Friedman D, Johnson R, Jr. (2000) Event-related potential (ERP) studies of memory encoding and retrieval: a selective review. Microsc. Res. Tech. 51: 6-28

Friston KJ (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2: 56-78

Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD Frackowiak RSJ (1995a) Spatial registration and normalisation of images. Hum. Brain Mapp 2: 165-189

Friston KJ, Büchel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997) Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6: 218-229

Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998b) Event-related fMRI: Characterizing differential responses. NeuroImage 7: 30-40

Friston KJ, Holmes AP, Worsely KJ, Poline J-B, Frith CD, Frackowiak RSJ (1995b) Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 2: 189-210

Friston KJ, Josephs O, Rees G, Turner R (1998a) Nonlinear event-related responses in fMRI. Mag Res Med 39: 41-52

Friston K.J, Penny W, Phillips C, Kiebel S, Hinton G, Ashburner J (2002) Classical and Bayesian Inference in Neuroimaging: Theory. Neuroimage 16(2): 465-483

Funayama ES, Grillon C, Davis M, Phelps EA (2001) A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. J Cogn Neurosci. 13(6): 721-729

Gabrieli JD, Brewer JB, Desmond JE, Glover GH (1997) Separate neural bases of two fundamental memory processes in the human medial temporal lobe. Science 276(5310): 264-266

Garavan H, Pendergrass JC, Ross TJ, Stein EA, Risinger RC (2001) Amygdala response to both positively and negatively valenced stimuli. Neuroreport. 12(12): 2779-2783

Gardiner JM, Ramponi C, Richardson-Klavehn A (1999) Response deadline and subjective awareness in recognition memory. Consc Cogn 8(4): 484-496

Gemar MC, Kapur S, Segal ZV, Brown GM, Houle S (1996) Effects of self-generated sad mood on regional cerebral activity: a PET study in normal subjects. Depression. 4(2): 81-88

Gentile CG, Jarrell TW, Teich A, McCabe PM, Schneiderman N (1986) The role of amygdaloid central nucleus in the retention of differential pavlovian conditioning of bradycardia in rabbits. Behav Brain Res. 20(3): 263-273

Gershberg FB, Shimamura AP (1995) Impaired use of organizational strategies in free recall following frontal lobe damage. Neuropsychologia 33(10): 1305-1333

Gevins A, Leong H, Smith ME, Le J, Du R (1995) Mapping cognitive brain function with modern high-resolution electroencephalography. Trends Neurosci 18(10): 429-436

Gillig P, Sackellares JC, Greenberg HS (1988) Right hemisphere partial complex seizures: mania, hallucinations and speech disturbances during ictal events. Epilepsia 29(1): 26-29

Glanzer, M., Kim, K., Hilford, A. & Adams, J. K. 1999 Slope of the receiver operating characteristic in recognition memory. J. Exp. Psychol. Learn.Mem. Cogn. 25, 500-513

Gläscher J, Adolphs R (2003) Processing of the arousal of subliminal and supraliminal emotional stimuli by the human amygdala. J Neurosci. 23(32): 10274-10282

Glaser EM, Ruchkin DS (1976) Principles of neurobiological signal analysis. New York: Academic Press

Gottfried JA, O'Doherty J, Dolan RJ (2002) Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. J Neurosci. 22(24): 10829-10837

Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. Science. 301(5636): 1104-1107

Gottfried JA, Smith AP, Rugg MD, Dolan RJ (2004) Remembrance of odors past: human olfactory cortex in cross-modal recognition memory. Neuron 42(4): 687-695

Grace AA, Rosenkranz JA (2002) Regulation of Conditioned Responses of Basolateral Amygdala Neurons. Phys. & Behav. 77: 489-493

Graf P, Schacter DL (1985) Implicit and explicit memory for new associations in normal and amnesic subjects. J. Exp. Psychol: Learn Mem Cogn 11: 501-518

Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RSJ, Dolan RJ (1993) Functional mapping of brain areas implicated in auditory-verbal memory function. Brain 116: 1-20

Greba Q, Kokkinidis L (2000) Peripheral and intraamygdalar administration of the dopamine D1 receptor antagonist SCH 23390 blocks fear-potentiated startle but not shock reactivity or the shock sensitization of acoustic startle. Behav Neurosci. 114(2): 262-272

Greenwald MK, Cook EW, Lang PJ (1989) Affective judgment and psychophysical response: dimensional covariation in the evaluation of pictorial stimuli. J Psychophysiol 3: 51-64

Gruppuso V, Lindsay DS, Kelley CM (1997) The process-dissociation procedure and similarity: defining and estimating recollection and familiarity in recognition memory. J Exp Psychol Learn Mem Cogn 23(2): 259-278

Halgren E, Wilson CL, Stapleton JM (1985) Human medial temporal lobe stimulation disrupts both formation and retrieval of recent memories. Brain Cogn 4(3): 287-295.

Hamann SB (2001) Cognitive and Neural Mechanisms of Emotional Memory. TICS 5(9): 394-400

Hamann SB, Cahill L, Squire LR (1997) Emotional perception and memory in amnesia. Neuropsychology 11(1): 104-113

Hamann SB, Ely TD, Grafton ST, Kilts CD (1999) Amygdala activity related to enhanced memory for pleasant and aversive stimuli. Nat.Neurosci. 2: 289-293

Hamann SB, Mao H (2002) Positive and negative emotional verbal stimuli elicit activity in the left amygdala. Neuroreport 13(1): 15-19

Hamann SB, Monarch ES, Goldstein FC (2000) Memory enhancement for emotional stimuli is impaired in early Alzheimer's disease. Neuropsychology 14(1): 82-92

Hariri AR, Mattay VS, Tessitore A, Fera F, Weinberger DR (2003) Neocortical modulation of the amygdala response to fearful stimuli. Biol Psychiatry 53(6): 494-501

Hasselmo ME, Wyble BP, Wallenstein GV (1996). Encoding and retrieval of episodic memories: role of cholinergic and GABAergic modulation in the hippocampus. Hippocampus 6(6): 693-708

Hebb DO (1949) The Organisation of Behaviour. New York: Wiley

Heeger DJ, Boynton GM, Demb JB, Seidemann E, Newsome WT (1999) Motion opponency in visual cortex. J Neurosci. 19(16): 7162-7174

Heeger DJ, Huk AC, Geisler WS, Albrecht DG (2000) Spikes versus BOLD: what does neuroimaging tell us about neuronal activity? Nat Neurosci. 3(7): 631-633

Henson RN (2003) Neuroimaging studies of priming. Prog Neurobiol 70(1): 53-81

Henson RN, Cansino S, Herron JE, Robb WG, Rugg MD (2003) A familiarity signal in human anterior medial temporal cortex? Hippocampus 13(2): 301-304

Henson RN, Rugg MD, Shallice T, Josephs O, Dolan RJ (1999a) Recollection and familiarity in recognition memory: An event-related functional magnetic resonance imaging study. J Neurosci. 19(10): 3962-3972

Henson RN, Rugg MD, Shallice T, Dolan RJ (2000) Confidence in recognition memory for words: Dissociating right prefrontal roles in episodic retrieval. J Cogn Neurosci. 12(6): 913-923

Henson RN, Shallice T, Dolan RJ (1999b) Right Prefrontal Cortex and Episodic Memory Retrieval: A functional MRI test of the Monitoring Hypothesis. Brain 122(7): 1367-1381

Herron JE, Henson RN, Rugg MD (2004) Probability effects on the neural correlates of retrieval success: an fMRI study. Neuroimage 21(1): 302-310

Herron JE, Rugg MD (2003) Retrieval orientation and the control of recollection. J Cogn Neurosci 15: 843-854

Herron JE, Wilding EL (2004) An electrophysiological dissociation of retrieval mode and retrieval orientation. Neuroimage 22(3): 1554-1562

Heuer F, Reisberg D (1990) Vivid memories of emotional events: the accuracy of remembered minutiae. Mem Cogn. 18(5): 496-506

Hicks JL, Marsh RL (1999) Remember-know judgements can depend on how memory is tested. Psych Bull Rev 6: 117-122

Hitchcock J, Davis M (1986) Lesions of the amygdala, but not of the cerebellum or red nucleus, block conditioned fear as measured with the potentiated startle paradigm. Behav Neurosci. 100(1): 11-22

Hintzman, DL (1986) `Schema abstraction' in a multiple trace memory model. Psychol. Rev. 94: 341-358

Hinztman DL, Curran T (1994) Retrieval dynamics of recognition and frequency judgements: evidence for separate processes of familiarity and recall. J Mem Lang 33(1): 1-18

Hintzman DL, Caulton DA, Levitin DJ (1998) Retrieval dynamics in recognition and list discrimination: further evidence for separate processes of familiarity and recall. Mem Cogn 26(3): 449-462

Holdstock JS, Mayes AR, Roberts N, Cezayirli E, Isaac CL, O'Reilly RC, Norman KA (2002) Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? Hippocampus 12(3): 341-351

Hornak J, Rolls ET, Wade D (1996) Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage.
Neuropsychologia. 34(4): 247-261

Horwitz B (2003) The elusive concept of brain connectivity. Neuroimage 19: 466-470

Hunt GE, McGregor IS (1998) Contrasting effects of dopamine antagonists and frequency reduction on Fos expression induced by lateral hypothalamic stimulation. Behav Brain Res. 132(2): 187-201

Huppert F, Piercy M (1976) Recognition memory in amnesic patients: effects of temporal context and familiarity of material. Cortex 12: 3-20

Israel L, Schacter DL (1997) Pictorial encoding reduces false recognition of semantic associates. Psychon Bull Rev 4(4): 577-581

Ito R, Dalley JW, Robbins TW, Everitt BJ (2002) Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. J Neurosci. 22(14): 6247-6253

Jacoby LL (1991) A process dissociation framework: separating automatic from intentional uses of memory. J. Mem. Lang. 30: 513-541

Jacoby LL (1999) Ironic effects of repetition: measuring age-related differences in memory. J Exp Psych Learn Mem Cogn 25(1): 3-22

Jacoby LL, Dallas M (1981) On the relationship between autobiographical memory and perceptual learning. J. Exp.Psychol. Gen. 110: 306-340

Jacoby LL, Jones TC, Dolan PO (1998) Two effects of repetition: support for a dual-process model of knowledge judgments and exclusion errors. Psychon Bull Rev 5(4): 705-709

James W (1890) Principles of psychology. New York: Henry Holt & Co.

Janowsky JS, Shimamura AP, Kritchevsky M, Squire LR (1989) Cognitive impairment following frontal damage and its relevance to human amnesia. Behav Neurosci 103(3): 548-560

Jaspers HA (1958) The ten-twenty system of the international federation. Electroenceph Clin Neurophysiol 10: 371-375

Jenkins JH, Karno M (1992) The meaning of expressed emotion: theoretical issues raised by cross-cultural research. Am J Psychiatry 149(1): 9-21

Jervis BW, Coelho M, Morgan GW (1989) Effect on EEG responses of removing ocular artifacts by proportional EOG subtraction. Med Biol Eng Comp 27(5): 484-490

Johnson MK, Kounios J, Reeder JA (1994) Time-course studies of reality monitoring and recognition. J Exp Psychol Learn Mem Cogn 20(6): 1409-1419

Johnson RJ (1995) Event-related potential insights into the neurobiology of memory systems. In:, Handbook of neuropsychology, Vol. 10 (F Boller, J Grafman (Eds.)) pp. 135–163). Amsterdam: Elsevier

Johnson Jr. R, Pfefferbaum A, Kopell BS (1985) P300 and long-term memory: latency predicts recognition performance. Psycholphysiol 22(5): 497-507

Josephs O, Henson RNA (1999) Event-related fMRI: modelling inference and optimisation. Phil Trans R Soc Lond 354: 1215-1228

Kahn I, Davachi L, Wagner AD (2004) Functional-neuroanatomic correlates of recollection: implications for models of recognition memory. J Neurosci. 24(17): 4172-4180

Kalivas PW, Nakamura M (1999) Neural systems for behavioral activation and reward.
Curr Opin Neurobiol. 9(2): 223-227

Kandel ER (1989) Genes, nerve cells and the remembrance of things past. J Neuropsychiatry 1: 103-125

Kapur N, Friston KJ, Young A, Frith CD, Frackowiak RS (1995) Activation of human hippocampal formation during memory for faces: a PET study. Cortex 31(1): 99-108

Karayandis F, Andrews S, Ward PB, McConaghy N (1991) Effects of iter-item lag on word repetition: an event-related potential study. Psychophysiol 28: 307-318

Karis D, Fabiani M, Donchin E (1984) P300 and memory: individual differences in the von Restorff effect. Cogn Psychol 16: 177-216

Kazui H, Mori E, Hashimoto M, Hirono N, Imamura T, Tanimukai S, Hanihara T, Cahill L (2000) Impact of emotion on memory. Controlled study of the influence of emotionally charged material on declarative memory in Alzheimer's disease. Br J Psychiatry 177: 343-347

Keil A, Bradley MM, Hauk O, Rockstroh B, Elbert T, Lang PJ (2002) Large-scale neural correlates of affective picture processing. Psychophysiology 39, 641-649

Kensinger EA, Brierley B, Medford N, Growdon JH, Corkin S (2002) Effects of normal aging and Alzheimer's disease on emotional memory. Emotion. 2(2): 118-134

Kensinger EA, Corkin S (2004) Two routes to emotional memory: distinct neural processes for valence and arousal. Proc. Natl. Acad. Sci. USA 101(9): 3310-3315

Keselman HJ, Rogan JC (1980) Repeated measures F tests and psychophysical research: controlling the number of false positives

Kilpatrick L, Cahill L (2003) Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. Neuroimage. 20(4): 2091-2099

Kim JJ, Fanselow MS (1992) Modality-specific retrograde amnesia of fear. Science 256(5057): 675-677

Kim JJ, Shih JC, Chen K, Chen L, Bao S, Maren S, Anagnostaras SG, Faneslow MS, De Maeyer E, Seif I, Thompson RF (1997) Selective Enhancement of Emotional, but not Motor, Learning in Monoamine Oxidase A-deficient Mice. Proc. Natl. Acad. Sci. USA 94(11): 5929-5933

Kluver H, Bucy PC (1939) Preliminary analysis of functions of the temporal lobes in monkeys. Arch. Neurol. Psychiat 42: 979–1000

Knight DC, Nguyen HT, Bandettini PA (2003) Expression of conditional fear with and without awareness. Proc Natl Acad Sci U S A. 100(25): 15280-15283

Knowlton BJ, Faneslow MS (1998) The hippocampus, consolidation and on-line memory. Curr Opin Neurobiol 8(2): 293-296

Knowlton BJ, Squire LR (1995) Remembering and knowing: two different expressions of declarative memory. J Exp Psychol Learn Mem Cogn 21(3): 699-710

Kolb B, Whishaw IQ (1980). Memory. In: Fundamentals of human neuropsychology (RC Atkinson, J Freedman, G Lindzey, RF Thompson (Eds.)) San Fransisco: W.H. Freeman and Co.

Konishi S, Wheeler ME, Donaldson DI, Buckner RL (2000) Neural correlates of episodic retrieval success. NeuroImage 12: 276– 286

Kopelman MD, Stanhope N, Kingsley D (1997) Temporal and spatial context memory in patients with focal frontal, temporal lobe, and diencephalic lesions. Neuropsychologia. 35(12): 1533-1545. Erratum in: Neuropsychologia 36(8): 796

Krawczyk DC (2002) Contributions of the Prefrontal Cortex to the Neural Basis of Human Decision Making. Neurosci. Biobehav. Rev. 26(6): 631-664

Kringelbach ML, Rolls ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol. 72(5): 341-372

Kroll NE, Knight RT, Metcalfe J,Wolf ES, Tulving E. (1996) Cohesion failure as a source of memory illusions. J. Mem. Lang. 35: 176–196

Kuniecki M, Urbanik A, Sobiecka B, Kozub J, Binder M (2003) Central Control of Heart Rate Changes During Visual Affective Processing as revealed by fMRI. Acta Neurobiol Exp (Wars) 63(1): 39-48

Kutas M, Dale AM (1997) Electrical and magnetic readings of mental functions. In Cognitive neuroscience (MD Rugg (Ed.)) East Sussex: Psychology Press

Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weiskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng H-M, Brady TJ, Rosen BR (1992) Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. Proc Natl Acad Sci USA 89: 5675-5679

LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. (1998) Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron. 20(5): 937-945

LaBar KS, LeDoux JE, Spencer DD, Phelps EA (1995) Impaired fear conditioning following unilateral temporal lobectomy in humans. J Neurosci. 15(10): 6846-6855

Lane RD, Chua PM, Dolan RJ (1999) Common Effects of Emotional Valence, Arousal and Attention on Neural Activation During Visual Processing of Pictures. Neuropsychologia 37(9): 989-997

Lang PJ, Bradley MM, Cuthbert BN (1990) Emotion, attention, and the startle reflex. Psychol Rev. 97(3): 377-395

Lang PJ, Bradley MM, Cuthbert BN (1997) The International Affective Picture System(IAPS): Photographic slides. Gainesville, Florida, University of Florida.

Lang PJ, Bradley MM, Fitzsimmons JR, Cuthbert BN, Scott JD, Moulder B, Nangia V (1998) Emotional arousal and activation of the visual cortex: an fMRI analysis. Psychophysiology 35: 199-210

Lang PJ, Greenwald MK, Bradley MM, Hamm AO (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30(3): 261-273

LeCompte DC (1995) Recollective experience in the revelation effect: separating the contributions of recollection and familiarity. Mem Cogn 23(3): 324-334.

LeDoux JE (2000) Emotion circuits in the brain. Annu Rev Neurosci. 23: 155-184

LeDoux JE, Cicchetti P, Xagoraris A, Romanski LM (1990) The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. J Neurosci. 10(4): 1062-1069

LeDoux JE, Iwata J, Cicchetti P, Reis DJ (1988) Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. J Neurosci. 8(7): 2517-2529

Lewis PA, Critchley HD. Mood-dependent memory. Trends Cogn Sci 7(10): 431-433

Liang KC, Hon W, Tyan YM, Liao WL (1994) Involvement of hippocampal NMDA and AMPA receptors in acquisition, formation and retrieval of spatial memory in the Morris water maze. Chi J Physiol 37(4): 201-212

Liberzon I, Britton JC, Phan KL (2003) Neural correlates of traumatic recall in posttraumatic stress disorder. Stress 6(3): 151-156.

Lowe MJ, Mock BJ, Sorenson JA (1998) Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage 7: 119-132

Majidishad P, Pelli DG, LeDoux JE. (1996) Disruption of fear conditioning to contextual stimuli but not to a tone by lesions of the accessory basal nucleus of the amygdala. Soc. Neurosci. Abstr. 22: 1116

Mandler G (1980) Recognizing: the judgment of previous occurrence. Psychol. Rev. 87: 252-271

Mandler G (1991) Your face looks familiar but I can't remember your name: A review of dual process theory. In: Relating theory and data: essays on human memory in honour of Bennet B. Murdock (W.E. Hockley, E.S. Lewandowsky (Eds.)) pp 207-225 NJ: Hillsdale

Mangels JA (1997) Strategic processing and memory for temporal order in patients with frontal lobe lesions. Neuropsychology 11(2): 207-221

Mangels JA, Picton TW, Craik FIM (2001) Attention and successful episodic encoding: an event-related potential study. Cogn Brain Res 11(1): 77-95

Manns JR, Hopkins RO, Reed JM, Kitchener EG, Squire LR (2003) Recognition memory and the human hippocampus. Neuron 37(1): 171-180

Mansfield P (1977) Multi-planar image formation using NMR spin echoes. J Physiol (Lond) 10: 349-352

Maratos EJ, Allan K, Rugg MD (2000) Recognition memory for emotionally negative and neutral words: an ERP study. Neuropsychologia 38(11): 1452-1465

Maratos EJ, Rugg MD (2001). Electrophysiological correlates of the retrieval of emotional and non- emotional context. J. Cogn Neurosci. 13: 877-891

Maratos EJ, Dolan RJ, Morris JS, Henson RN, Rugg MD (2001). Neural activity associated with episodic memory for emotional context. Neuropsychologia 39: 910-920

Maren S (2001) Neurobiology of Pavlovian fear conditioning. Annu Rev Neurosci. 24: 897-931

Maren S, Aharonov G, Fanselow MS (1997) Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. Behav Brain Res. 88(2): 261-274

Maren S, Fanselow MS (1995) Synaptic plasticity in the basolateral amygdala induced by hippocampal formation stimulation in vivo. J Neurosci. 15(11): 7548-7564

Markowitsch HJ (1999) The limbic system. In: The MIT encyclopaedia of cognitive science (R Wilson, K Keil (Eds.)) pp 470-472. Cambridge, Massachusetts: MIT Press.

Markowitsch HJ (2000) The anatomical basis of memory. In: The New Cognitive Neurosciences (MS Gazzaniga (Ed.)) pp 765-780. Cambridge, Massachusetts: MIT Press

Markowitsch HJ, Vandekerckhovel MM, Lanfermann H, Russ MO (2003) Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. Cortex 39(4-5): 643-665

Marr D (1971) Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci. 262(841): 23-81

Mayes AR, Baddeley AD, Cockburn J, Meudell PR (1989) Why are amnesic judgements of recency and frequency made in a qualitatively different way from those of normal people? Cortex 25(3): 479-488

Mayes AR, Isaac CL, Holstock JS, Hunkin NM, Montaldi D, Downes JJ, MacDonald C, Cezayirili E, Roberts JN (2001) Memory for single items, word pairs and temporal order of different kinds in a patient with selective hippocampal lesions. Cogn Neuropsych 18(2): 97-123

McCarthy,G. & Wood,C.C. (1985). Scalp distributions of event-related potentials: an ambiguity associated with analysis of variance models. Electroencephalogr. Clin. Neurophysiol. 62: 203-208

McDermott KB, Jones TC, Petersen SE, Lageman SK, Roediger HL (2000) Retrieval success is accompanied by enhanced activation in anterior prefrontal cortex during recognition memory: An event-related fMRI study. J. Cogn. Neurosci. 12: 965– 976

McDonald AJ (1997) Calbindin-D28k immunoreactivity in the rat amygdala. J Comp Neurol. 383(2): 231-244

McGaugh J.L, Cahill L. & Roozendaal B. (1996) Involvement of the Amygdala in Memory Storage: Interaction with Other Brain Systems. Proc. Natl. Acad. Sci. USA 93(24): 13508-13514

McIntosh AR, Gonzalez-Lima F (1991) Structural modelling of functional neural pathways mapped with 2-deoxyglucose: effect of acoustic startle habituation on the auditory system. Brain Res 547: 295-302

McIntosh AR, Grady CL, Underleider LG, Haxby JV, Rapoport SI, Horwitz B (1994) Network analysis of cortical visual pathways mapped with PET. J Neurosci 14: 655-666

Mechelli A, Penny WD, Price CJ, Gitelman DR, Friston KJ (2002) Effective connectivity and intersubject variability: using a multisubject network to test differences and commonalities. Neuroimage 17: 1459-1469

Mecklinger A, von Cramon DY, Matthes-von Cramon G (1998) Event-related potential evidence for a specific recognition memory deficit in adult survivors of cerebral hypoxia.
Brain 121(10): 1919-1935

Michel CM, Thut G, Morand S, Khateb A, Pegna AJ, Grave de Peralta R, Gonzalez S, Seeck M, Landis T (2001) Electric source imaging of human brain functions. Brain Res Rev 36: 108-118

Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL (2000) Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. NeuroImage 11: 735–759

Milner B (1962) Les troubles de la memoire accompagnant les lesions hippocampiques bilaterales. In: Physiologie de l'Hippocampe, Colloques Internationaux No 107. pp 257-272. Paris: CNRS

Milner B (1966) Amnesia following operation on the temporal lobes. In Amnesia (CWM Whitty, OL Zangwill (Eds.)) pp. 109-133. London: Butterworths.

Mini A, Palomba D, Angrilli A, Bravi S (1996). Emotional information processing and visual evoked brain potentials. Percept. Mot. Skills 83: 143-152

Mintzner MZ, Griffiths RR (2000) Acute effects of triazolam on false recognition. Mem Cogn 28(8): 1357-1365

Mishkin M, Vargha-Khadem F, Gadian DG (1998) Amnesia and the organization of the hippocampal system. Hippocampus 8: 212-216

Morgan MA, Schulkin J, LeDoux JE (2003) Ventral medial prefrontal cortex and emotional perseveration: The memory for prior extinction training. Behav Brain Res. 146(1-2): 121-130

Morris JS, DeGelder B, Weiskrantz L, Dolan RJ (2001) Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. Brain. 124(6): 1241-1252

Morris JS, Friston KJ, Buchel C, Frith CD, Young AW, Calder AJ, Dolan RJ (1998b) A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain. 121 (1): 47-57

Morris JS, Ohman A, Dolan RJ (1998a) Conscious and unconscious emotional learning in the human amygdala. Nature. 393(6684): 467-470

Morris JS, Ohman A, Dolan RJ (1999) A subcortical pathway to the right amygdala mediating "unseen" fear. Proc Natl Acad Sci U S A. 96(4): 1680-1685

Mumby DG, Wood ER, Duva CA, Kornecook TJ, Pinel JPJ, Phillips AG (1996) Ischemia induced object-recognition deficits in rats are attenuated by hippocampal ablation before or soon after ischemia. Behav. Neurosci. 110: 266–281

Murdock BB (1982) A theory of storage and retrieval of item and associative information. Psychol. Rev. 89: 609-666

Murdock BB, Dufty PO (1972) Strength theory and recognition memory. J. Exp. Psychol. Gen. 94: 284-290

Nadel L, Moscovitch M (1997) Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 7(2): 217-227

Nadel L, Moscovitch M (1998) Hippocampal contributions to cortical plasticity. Neuropharmacology 27(4-5): 431-439

Nadel L, Moscovitch M (2001) The hippocampal complex and long-term memory revisited. Trends Cogn Sci. 5(6): 228-230

Nader K, LeDoux JE (1999) Inhibition of the mesoamygdala dopaminergic pathway impairs the retrieval of conditioned fear associations. Behav Neurosci. 113(5): 891-901

Nader K, Schafe GE, LeDoux JE (2000) Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature. 406(6797):722-726

Nessler D, Mecklinger A, Penney TB (2001). Event related brain potentials and illusory memories: the effects of differential encoding. Cogn Brain Res 10: 283–301

Neville HJ, Kutas M, Chesney G, Schmidt AL (1986) Event-related brain potentials during initial encoding and recognition memory of congruous and incongruous words. J Mem Lang 25: 75-92

Nuñez PL (1990) Localisation of brain activity with EEG. Adv Neurol 54: 39-65

Nyberg L, Persson J, Habib R, Tulving E, McIntosh AR, Cabeza R, Houle S (2000) Large scale neurocognitive networks underlying episodic memory. J Cogn Neurosci. 12(1): 163-173

Nyberg L, Tulving E, Habib R, Nilsson LG, Kapur S, Houle S, Cabeza R, McIntosh AR (1995) Functional brain maps of retrieval mode and recovery of episodic information.
Neuroreport 7(1): 249-252

O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004) Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 304(5669): 452-454

O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ (2002) Neural responses during anticipation of a primary taste reward. Neuron 33(5): 815-826

O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001) Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci. 4(1): 95-102

O'Keefe J, Dostrovsky J (1971) The hippocampus as a spatial map: preliminary evidence from unit activity in the freely-moving rat. Brain Res. 34: 171–75

O'Keefe J, Nadel L (1978) The Hippocampus as a Cognitive Map. Oxford, UK: Oxford Univ. Press

Ogawa S, Lee T-M (1990) Magnetic resonance imaging of blood vessels at high fields: in vivo and in vitro measurements and image simulation. Magn Res Med 16: 9-18

Ogawa S, Lee T-M, Nayak AS, Glynn P (1990) Oxygenation-sensitive contrast inmagnetic resonance image of rodent brain at high magnetic fields. Magn Res Med 14: 68-78

Ogawa S, Tank DW, Menon R, Ellerman JM, Kim S-G, Merkle H, Ugurbil K (1992) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 89: 5951-5955

Ohman A, Flykt A, Esteves F (2001) Emotion drives attention: detecting the snake in the grass. J Exp Psychol Gen 130(3): 466-478

Ortony A, Turner TJ (1990) What's basic about basic emotions? Psychol Rev. 97(3): 315-331

Oshiro Y, Fuijita N, Tanaka H, Hirabuki N, Nakamura H, Yoshiya I (1998) Functional mapping of pain-related activation with echo-planar MRI: significance of the SII-insular region. Neuroreport 9(10): 2285-2289

Otten LJ, Henson RNA, Rugg MD (2001) Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain 124(2): 399-412

Otten LJ, Henson RNA, Rugg MD (2002) State-related and item-related neural correlates of successful memory encoding. Nat. Neurosci. 5(12): 1339-1344

Palomba D, Angrilli A, Mini A (1997). Visual evoked potentials, heart rate responses and memory to emotional pictorial stimuli. Int. J. Psychophysiol. 27: 55-67

Panksepp J (1992) A critical role for 'affective neuroscience' in resolving what is basic about emotions. Psychol Rev 99(3): 554-560

Papez JW (1937) A proposed mechanism of emotion. Arch Neurol Psychiat (Chicago) 38: 725-743

Pardo JV, Pardo PJ, Raichle ME (1993) Neural correlates of self-induced dysphoria. Am J Psychiatry. 150(5): 713-719

Patterson DW, Schmidt LA (2003) Neuroanatomy of the human affective system. Brain Cogn. 52(1): 24-26

Pauling L, Coryall CD (1936) The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonoxyhemoglobin. Proc Natl Acad Sci USA 22: 210-216

Pavlov I (1927) Conditioned reflexes. New York: Dover

Penny WD, Holmes A (2003) Random Effects Analysis. In: Human Brain Function II (RSJ Frackowiak et al (Eds.)) London: Elsevier

Peterson LR, Peterson MJ (1959) Short-term retention of individual verbal items. J. Exp. Psychol. 58: 193-198

Peyron R, Laurent B, Garcia-Larrea L (2000) Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin. 30(5): 263-88

Pfurtscheller G, Andrew C (1999) Event-related changes of band power and coherence: methodology and interpretation. J. Clin. Neurophysiol 16: 512-519

Picton TW, Bentin S, Berg P, Donchin E, Hillyard SA, Johnson R, Miller GA, Ritter W, Ruchkin DS, Rugg MD, Taylor MJ (2000) Guidelines for using human event-related potentials to study cognition: recording standards and publication criteria. Psychophysiology 37(2): 127-152

Piefke M, Weiss PH, Zilles K, Markowitsch HJ, Fink GR (2003) Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory.
Brain. 126(3): 650-668

Phan KL, Taylor SF, Welsh RC, Decker LR, Noll DC, Nichols TE, Britton JC, Liberzon I (2003) Activation of the Medial Prefrontal Cortex and Extended Amygdala by Individual Ratings of Emotional Arousal: a fMRI Study. Biol. Psychiatry 53(3): 211-215

Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional Neuroanatomy of Emotion: a Meta-analysis of Emotion Activation Studies in PET and fMRI. Neuroimage 16(2): 331-348

Phan KL, Wager TD, Taylor SF, Liberzon I (2004) Functional neuroimaging studies of human emotions. CNS Spectr. 9(4): 258-266

Phelps EA (2004) Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol. 14(2): 198-202

Phelps EA, LaBar KS (1997) The role of organisation in recall for affective words. Abstr Psychonomic Soc 2: 4-5

Phelps EA, LaBar KS, Anderson AK, O'Connor KJ, Fulbright RK, Spencer DD (1998) Specifying the Contributions of the Human Amygdala to Emotional Memory: A Case Study. Neurocase 4: 527-540

Phelps EA, LaBar KS, Spencer DD (1997) Memory for emotional words following unilateral temporal lobectomy. Brain Cogn. 35(1): 85-109

Phelps EA, O'Connor KJ, Gatenby JC, Gore JC, Grillon C, Davis M (2001) Activation of the Left Amygdala to a Cognitive Representation of Fear. Nat. Neurosci. 4(4): 437-441

Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, Williams SC, Bullmore ET, Brammer M, Gray JA (1998) Neural responses to facial and vocal expressions of fear and disgust. Proc R Soc Lond B Biol Sci. 265(1408): 1809-1817

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SC, Gray JA, David AS (1997) A Specific Neural Substrate for Perceiving Facial Expressions of Disgust. Nature 389(6650): 495-498

Phillips RG, LeDoux JE (1992) Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci. 106(2): 274-285

Pitkanen A, Savander V, LeDoux JE (1997) Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends Neurosci. 20(11): 517-523

Potter DD, Pickles CD, Roberts RC, Rugg MD (1992) The effects of scopolamine on event-related potentials in a continuous recognition memory task. Psychophysiology 29(1):29-37

Prabhakaran V, Smith JA, Desmond JE, Glover GH, Gabrieli JD (1997) Neural substrates of fluid reasoning: an fMRI study of neocortical activation during performance of the Raven's Progressive Matrices Test. Cognit. Psychol. 33(1): 43-63

Pratt WE, Mizumori SJ (1998) Characteristics of basolateral amygdala neuronal firing on a spatial memory task involving differential reward. Behav Neurosci. 112(3): 554-570

Pratt WE, Mizumori SJ (2001) Neurons in rat medial prefrontal cortex show anticipatory rate changes to predictable differential rewards in a spatial memory task. Behav Brain Res 123(2): 165-183

Price C.J. (2000) The Anatomy of Language: Contributions from Functional Neuroimaging. J. Anat. 197(3): 335-359

Purcell EM, Torrey HC, Pound RV (1945) Resonance absorption by nuclearmagnetic moment. Phys Rev 69: 37-38

Quirk GJ & Gehlert DR (2003) Inhibition of the Amygdala: Key to Pathological States? Ann N Y Acad Sci. 985: 263-72

Raichle ME (1987) Circulatory and metabolic correlates of brain function in normal humans. In Handbook of physiology: the nervous system. Baltimore: Williams and Wilkins

Rajaram S (1993) Remembering and knowing: two means of access to the personal past. Mem. Cogn. 21: 89-102

Reed JM, Squire LR (1997) Impaired recognition in patients with lesions limited to the hippocampal formation. Behav Neurosci 111: 667-675

Reed JM, Squire LR (1998) Retrograde amnesia for facts and events: Findings from four new cases. J Neurosci 18: 3943-3954

Rees G, Friston K, Koch C (2000) A direct quantitative relationship between the functional properties of human and macaque V5. Nat Neurosci 3(7): 716-723

Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, Yun LS, Chen K (1997) Neuroanatomical correlates of externally and internally generated human emotion. Am J Psychiatry. 154(7): 918-925

Rempel-Clower NL, Zola SM, Squire LR, Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J. Neurosci 16: 5233-5255

Richardson MP, Strange BA, Dolan RJ (2004) Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nat Neurosci 7(3): 278-285

Richter-Levin G (2004) The amygdala, the hippocampus, and emotional modulation of memory. Neuroscientist 10(1): 31-39

Richter-Levin G, Akirav I (2000) Amygdala-hippocampus dynamic interaction in relation to memory. Mol Neurobiol 22(1-3): 11-20

Richter-Levin G, Akirav I (2003) Emotional tagging of memory formation--in the search for neural mechanisms. Brain Res Rev 43(3): 247-256

Riedel G, Michaeu J, Lam AG, Roloff E, Martin SJ, Bridge H, Hoz L, Poeschel B, McCulloch J, Morris RG (1999) Reversible neural inactivation reveals hippocampal participation in several memory processes. Nat Neurosci 2(10): 898-905

Robinson RG, Chait RM (1985) Emotional correlates of structural brain injury with particular emphasis on post-stroke mood disorders. Crit Rev Clin Neurobiol 1(4): 285-318

Rogan MT, LeDoux JE (1995) LTP is accompanied by commensurate enhancement of auditory-evoked responses in a fear conditioning circuit. Neuron 15(1): 127-136

Rogan MT, Staubli UV, LeDoux JE (1997) Fear conditioning induces associative long-term potentiation in the amygdala. Nature 390(6660): 604-607. Erratum in: Nature 391(6669): 818

Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, Robbins TW (1999) Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. J Neurosci. 19(20): 9029-9038

Rolls ET (2000) The orbitofrontal cortex and reward. Cereb Cortex 10(3): 284-294

Rolls ET, Burton MJ, Mora F (1980) Neurophysiological analysis of brain-stimulation reward in the monkey. Brain Res. 194(2): 339-357

Rolls ET, Hornak J, Wade D, McGrath J (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry. 57(12): 1518-1524

Rolls ET, Stringer SM (2001) A model of the interaction between mood and memory. Network 12(2): 89-109

Rombouts SA, Barkhof F, Witter MP, Machielsen WC, Scheltens P (2001) Anterior Medial Temporal Lobe Activation During Attempted Retrieval of Encoded Visuospatial Scenes: and Event-related fMRI Study. Neuroimage 14(1): 67-76

Rosenkranz JA, Grace AA (2001) Dopamine Attenuates Prefrontal Cortical Suppression of Sensory Inputs to the Basolateral Amygdala of Rats. J. Neurosci. 21(11): 4090-4103

Rugg MD, Allan K (2000) Memory retrieval: An electrophysiological perspective. In Gazzaniga, M. S.(Ed.) The New Cognitive Neurosciences (2nd Ed.) pp. 805-816. Cambridge, MIT Press

Rugg MD, Allan K, Birch CS (2000) Electrophysiological evidence for the modulation of retrieval orientation by depth of study processing. J Cogn Neurosci. 12(4):664-678

Rugg MD, Coles MGH (Eds.) (1995) Electrophysiology of mind: event-related brain potentials and cognition. Oxford: Oxford University Press

Rugg MD, Cox CJ, Doyle MC, Wells T (1995) Event-related potentials and the recollection of low and high frequency words. Neuropsychologia 33(4): 471-484

Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ (1996) Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. Brain 119(6): 2073-2083

Rugg MD, Fletcher PC, Frith CD, Frackowiak RS, Dolan RJ (1997a). Brain regions supporting intentional and incidental memory: a PET study. Neuroreport 8(5): 1283-1287

Rugg MD, Henson RN, Robb WG (2003) Neural correlates of retrieval processing in the prefrontal cortex during recognition and exclusion tasks. Neuropsychologia. 41(1): 40-52

Rugg MD, Mark RE, Gilchrist J, Roberts RC (1997b) ERP repetition effects in indirect and direct tasks: effects of age and interim lag. Psychophysiology 34(5): 572-586.

Rugg MD, Mark RE, Walla P, Schloerscheidt AM, Birch CS, Allan K (1998) Dissociation of the neural correlates of implicit and explicit memory. Nature 392(6676): 595-598

Rugg MD, Nagy ME (1987) Lexical contribution to nonword-repetition effects: evidence from event-related potentials. Mem Cogn. 15(6): 473-481.

Rugg MD, Nagy ME (1989) Event-related potentials and recognition memory for words.
Electroenceph Clin Neurophysiol. 72(5): 395-406

Rugg MD, Otten LJ, Henson RN (2002) The neural basis of episodic memory: evidence from functional neuroimaging. Phil Trans R Soc Lond B Biol Sci. 357(1424): 1097-1110

Rugg MD, Wilding EL (2000) Retrieval processing and episodic memory. Trends Cog Sci 4: 108-115

Rugg MD, Yonelinas AP (2003) Human recognition memory: a cognitive neuroscience perspective. Trends Cogn. Sci. 7: 313–319

Sackeim HA, Greenberg MS, Weiman AL, Gur RC, Hungerbuhler JP, Geschwind N (1982) Hemispheric asymmetry in the expression of positive and negative emotions. Neurologic evidence. Arch Neurol. 39(4): 210-218

Sakai K (2003) Reactivation of memory: role of medial temporal lobe and prefrontal cortex. Rev Neurosci. 14(3): 241-252

Schacter DL, Alpert NM, Savage CR, Rauch SL, Alpert MS (1996) Conscious recollection and the human hippocampal formation: evidence from positron emission tomography. Proc Natl Acad Sci USA 93: 321-325

Schacter, DL, Buckner RL, Koutstaal W, Dale AM, Rosen BR (1997) Late onset of anterior prefrontal activity during true and false recognition: an event-related fMRI study. NeuroImage 6: 259– 269

Schacter DL, Tulving E (1994) What are the memory systems of 1994? In: Memory Systems 1994. (Schacter DL, Tulving E (Eds)), pp 1-38 Cambridge MA: MIT Press

Schultz W, Apicella P, Ljungberg T (1993) Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci. 13(3): 900-913

Schultz W, Tremblay L, Hollerman JR (1998) Reward prediction in primate basal ganglia and frontal cortex. Neuropharmacology 37(4-5): 421-429

Schuman EM, Madison DV (1991) A requirement for the intracellular messenger nitric oxide in long-term potentiation. Science 254: 1503-1506

Schupp HT, Cuthbert BN, Bradley MM, Cacioppo JT, Ito T, Lang PJ (2000). Affective picture processing: the late positive potential is modulated by motivational relevance. Psychophysiology 37: 257-261

Scoville WB, Correll RE (1973) Memory and the temporal lobe. A review for clinicians. Acta Neurochirurgica 28(4): 251-258

Scoville WB, Milner B (1957) Loss of recent memory after bilateral hippocampal lesions. J Neurosurg Psychiat 20: 11-21

Seidenbecher T., Laxmi T.R., Stork O. & Pape HC. (2003) Amygdalar and hippocampal theta rhythm synchronization during fear memory retrieval. Science. 301(5634): 846-50.

Senkfor AJ, Van Petten C (1998) Who said what? An event-related potential investigation of source and item memory. J Exp Psychol Learn Mem Cogn 24(4): 1005-25

Shallice T, Burgess P (1996) The domain of supervisory processes and temporal organization of behaviour. Phil Trans R Soc Lond 351(1346): 1405-1411

Shallice T, Warrington EK (1970) Independent functioning of verbal memory stores: a neuropsychological study. Q J Exp Psychol 22: 261-273

Shallice T, Fletcher PC, Frith CD, Grasby P, Frackowiak RSJ, Dolan RJ (1994) Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature 368: 633-635

Shaver P, Schwartz J, Kirson D, O'Connor C (1987) Emotion knowledge: further exploration of a prototype approach. J Pers Soc Psych 52(6): 1061-1086

Siebert M, Markowitsch HJ, Bartel P (2003) Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. Brain. 126(12): 2627-2637

Smith APR, Henson RNA, Dolan RJ, Rugg MD (2004) fMRI correlates of the retrieval of emotional context. Neuroimage 22(2): 868-878

Smith APR, Dolan RJ, Rugg MD (2004) Event-related potential correlates of the retrieval of emotional and non-emotional contexts. J Cogn Neurosci 16(5): 760-775

Smith ME (1993) Neurophysiological manifestations of recollective experience during recognition memory judgments. Journal of CognitiveNeuroscience 5: 1–13

Smith ME, Halgren E (1989) Dissociation of recognition memory components following temporal lobe lesions. J Exp Psychol Learn Mem Cogn 15: 50-60

Spiers HJ, Maguire EA, Burgess N (2001) Hippocampal amnesia. Neurocase. 7(5): 357-382

Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H (1998) Neural structures associated with recognition of facial expression of basic emotions. Proc R Soc Lond B Biol Sci 265(1409): 1927-1931

Squire LR, Knowlton BJ (2000) The medial temporal lobe, the hippocampus and the memory systems of the brain. In: The New Cognitive Neurosciences (MS Gazzaniga (Ed.)) pp 765-780. Cambridge, Massachusetts: MIT Press

Squire LR, Stark CE, Clark RE (2004) The medial temporal lobe. Ann Rev Neurosci. 27: 279-306

Squire LR, Zola SM (1996) Structure and function of declarative and nondeclaritive memory systems. Proc Nat Acad Sci USA 93(24): 13515-13522

Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253: 1380-1386.

Stark CE, Okado Y (2003) Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. J Neurosci. 23(17): 6748-6753

Stark CE, Squire LR (2000) fMRI activity in the medial temporal lobe during recognition memory as a function of study-test interval. Hippocampus 10(3): 329-337

Stark CE, Squire LR (2001) Simple and associative recognition memory in the hippocampal region. Learn Mem. 8(4): 190-197

Stark CE, Squire LR (2003) Hippocampal damage equally impairs memory for single items and memory for conjunctions. Hippocampus 13(2): 281-292

Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A. 93(16): 8660-8665

Stewart J (1983) Conditioned and unconditioned drug effects in relapse to opiate and stimulant drug self-adminstration. Prog Neuropsychopharmacol Biol Psychiatry. 7(4-6): 591-597

Strange BA, Hurlemann R, Dolan RJ (2003) An emotion-induced retrograde amnesia in humans is amygdala- and beta-adrenergic-dependent. Proc Natl Acad Sci U S A. 100(23): 13626-13631

Tabert MH, Borod JC, Tang CY, Lange G, Wei TC, Johnson R, Nusbaum AO, Buchsbaum MS (2001). Differential amygdala activation during emotional decision and recognition memory tasks using unpleasant words: an fMRI study. Neuropsychologia 39: 556-573

Talairach J, Tournoux P (1988) Co-planar Stereotaxic Atlas of the Human Brain. Stuttgart: Thieme

Taylor SF, Liberzon I, Fig LM, Decker LR, Minoshima S, Koeppe RA (1998) The effect of emotional content on visual recognition memory: A PET activation study. Neuroimage 8(2): 188-197

Teasdale JD, Howard RJ, Cox SG, Ha Y, Brammer MJ, Williams SC, Checkley SA (1999) Functional MRI Study of the Cognitive Generation of Affect. Am. J. Psychiatry 156(2): 209-215

Thompson RF (1976). The search for the engram. Am Psychol 31(3): 209-227

Tobler PN, Dickinson A, Schultz W (2003) Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. J Neurosci. 23(32): 10402-10410

Toth JP (1996) Conceptual automaticity in recognition memory: levels-of-processing effects on familiarity. Can. J.Exp. Psychol. 50: 123-138

Tulving E (1983). Elements of episodic memory. Oxford University Press.

Tulving E (1985) Memory and consciousness.Can.Psychol. 26: 1-12

Tulving E (1993) What is episodic memory? Curr Dir Psych Sci 2(3): 67-70

Tulving E (2002) Episodic memory: from mind to brain. Annu Rev Psychol. 53: 1-25

Tulving E, Kapur S, Craik FIM, Moscovitch M, Houle S (1994) Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Nat Acad Sci USA 91(6): 2016-2020

Tulving E, Markowitsch HJ (1998) Episodic and declarative memory: Role of the hippocampus. Hippocampus 8(3): 198-204

Turner BH, Mishkin M, Knapp M (1980) Organization of the amygdalopetal projections from modality-specific cortical association areas in the monkey. J Comp Neurol. 191(4): 515-543

Urbach TP, Kutas M (2002) The intractability of scaling scalp distributions to infer neuroelectric sources. Psychophysiology 39(6): 791-808

Vaidya CJ, Zhao M, Desmond JE, Gabrieli JD (2002) Evidence for cortical encoding specificity in episodic memory: memory-induced re-activation of picture processing areas. Neuropsychologia 40(12): 2136-2143

Van de Kar LD, Piechowski RA, Rittenhouse PA, Gray TS (1991) Amygdaloid lesions: differential effect on conditioned stress and immobilization-induced increases in corticosterone and renin secretion. Neuroendocrinology 54(2): 89-95

Van Petten C, Luka BJ, Rubin SR, Ryan JP (2002). Frontal brain activity predicts individual performance in an associative memory exclusion test. Cereb. Cortex 12: 1180-1192

van Stegeren AH, Everaerd W, Gooren LJ (2002) The effect of beta-adrenergic blockade after encoding on memory of an emotional event. Psychopharmacology (Berl) 163(2): 202-212

van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS (2001) Anterior Cingulate Cortex, Conflict Monitoring and Levels of Processing. Neuroimage 14(6): 1302-1308

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Paesschen WV, Mishkin M (1997) Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277: 376-380

Verfaellie M (1995) Knowledge of new English vocabulary in amnesia: an examination of premorbidly acquired semantic memory. J. Int. Neuropsychol. Soc. 1: 443–453

Verfaellie M, Cermak LS (1999) Perceptual fluency as a cue for recognition judgments in amnesia. Neuropsychology 13(2): 198-205

Viskontas IV, McAndrews MP, Moscovitch M (2000) Remote episodic deficits in patients with unilateral temporal lobe epilepsy and excisions. J Neurosci 20(15): 5853-5857

Vuilleumier P, Armony JL, Driver J, Dolan RJ (2001). Effects of attention and emotion on face processing in the human brain: an event-related fMRI study. Neuron 30(3): 829-841

Wadghiri YZ, Johnson G, Turnbull DH (2001) Sensitivity and performance time in MRI dephasing artifact reduction methods. Magn Reson Med 45(3): 470-476

Waldvogel D, van Gelderen P, Muellbacher W, Ziemann U, Immisch I, Hallett M (2000) The relative metabolic demand of inhibition and excitation. Nature 406(6799): 995-998

Warrington E, Weiskrantz L (1968) New method of testing long-term retention with special reference to amnesic patients. Nature 217: 972-974

Weiskrantz L (1956) Behavioural Changes Associated with Ablation of the Amygdaloid Complex in Monkeys. J. Comp. Phys. Psychol. 49: 381-391

Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, Rauch SL (1998) The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. Biol Psychiatry 44(12): 1219-1228

Wheeler ME, Buckner RL (2003) Functional dissociation among components of remembering: control, perceived oldness, and content. J Neurosci. 23: 3869– 3880

Wheeler ME, Buckner RL (2004) Functional-anatomic correlates of remembering and knowing. Neuroimage 21(4): 1337-1349

Wheeler ME, Petersen SE, Buckner RL (2000) Memory's echo: vivid remembering reactivates sensory-specific cortex. Proc Natl Acad Sci U S A. 97(20): 11125-11129. Erratum in: Proc Natl Acad Sci U S A. 101(14): 5181

Whittlesea BWA, Jacoby LL, Girard K (1990) illusions of immediate memory: evidence of an attributional basis for feelings of familiarity and perceptual quality. J Mem Lang 29(6): 198-205

Whittlesea BWA, Williams LD (2000) The source of feelings of familiarity: the discrepancy-attribution hypothesis. J Exp Psych Learn Mem Cogn 26(3): 547-565

Wilding EL (2000) In what way does the parietal ERP old/new effect index recollection?
Int J Psychophysiol. 35(1): 81-87

Wilding EL, Doyle MC, Rugg MD (1995) Recognition memory with and without retrieval of context: an event-related potential study. Neuropsychologia 33(6): 743-767

Wilding EL, Rugg MD (1996) An event-related potential study of recognition memory with and without retrieval of source. Brain 119(3): 889-905

Willis M (2000) ERPS Lab computer software. Cognitive Electrophysiology Group.

Wood CC, Allison T (1981) Interpretation of evoked potentials: a neurophysiological perspective. Can J Psychol 35(2): 113-135

Woolrich MW, Ripley BD, Brady M, Smith SM (2001) Temporal autocorrelation in univariate linear modeling of fMRI data. Neuroimage 14(6): 1370-1386

Worsley KJ, Friston KJ (1995) Analysis of fMRI time series revisited – again. NeuroImage 2: 173-181

Yonelinas, AP (1994) Receiver-operating characteristics in recognition memory: evidence for a dual-process model. J. Exp. Psychol. Learn.Mem. Cogn. 20: 1341-1354

Yonelinas AP (2001) Consciousness, control and confidence: the 3 Cs of recognition memory. J Exp Psych Gen 130(3): 361-379

Yonelinas AP, Jacoby LL (1995) The relation between remembering and knowing as bases for recognition: effects of size congruency. J. Mem. Lang. 34: 622-643

Yonelinas AP, Kroll NEA, Dobbins IG, Soltani M (1999) Recognition memory for faces: when familiarity supports associative recognition judgments. Psychonom .Bull. Rev. 6: 654-661

Yonelinas AP, Kroll NEA, Quamme JR, Lazzara MM, Sauve MJ, Widaman KF, Knight RT. (2002) Effects of extensive temporal lobe damage or mild hypoxia on recollection and familiarity. Nat Neurosci. 5(11): 1236-1241

Zald DH (2003) The Human Amygdala and the Emotional Evaluation of Sensory Stimuli. Brain Res. Rev. 41(1): 88-123

Zola-Morgan S, Squire LR, Amaral DG, Suzuki W (1989) Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 9: 4355-4370